The Journal of Pediatrics

VOL. 30 MAY, 1947 No. 5

Original Communications

PRESIDENTIAL ADDRESS

JAY I. DURAND, M.D.
SEATTLE, WASH.

A YEAR ago, Dr. Sisson and Dr. Hubbard presented the Academy with plans for the Study of Child Health Services. This survey was to extend into every county of our forty-eight states. It called for investigation and a report on the work of every hospital, institution, and health agency, and the practice of every doctor and dentist caring for children. They presented a budget calling for a million dollar expenditure. Most of us were staggered and rather terrified at the magnitude of the undertaking. Our state chairmen and members accepted the challenge. They have worked conscientiously and with increasing enthusiasm.

Today the greater part of the work has been done, and its successful conclusion is in sight. In taking just pride in this achievement, we must acknowledge our debt to the United States Public Health Service, the Children's Bureau, The National Foundation for Infantile Paralysis, the evaporated milk and drug companies, and other agencies, whose generous aid with funds and personnel have made it possible.

The Academy must now assume the responsibility imposed by the survey. We must study its findings and assume leadership in utilizing them for the improvement of the health of America's children. To this end the Executive Board has created a new committee, the "Committee for the Improvement of Child Health," which will direct the work. Nine members have been appointed, three for a term of one year, and three for two and three years respectively. New members will be named for three years of service as the terms of the present appointees expire. This will provide continuity, with frequent infusion of new blood. Every member chosen for this service accepted promptly, a fine expression of our organization's unselfish desire to undertake welfare work. In addition to this national direction, state or local committees will no doubt carry on in many districts.

The threat of extremely socialistic legislation which sought to make us subservient to Federal bureaus and take the direction of work for the "Health

Presented before the Fifteenth Annual Meeting of the American Academy of Pediatrics, Pittsburgh, Pa., Feb. 24-27, 1947.

and Welfare of Children" out of our hands seems measurably eased. We are grateful to our legislative committee and its able chairman, Dr. Wall, for valuable work toward this end.

The improvement in the health and nutrition of children since I began the practice of pediatrics thirty-five years ago, is not appreciated by younger graduates, and perhaps has been forgotten by some of the older men. In the early days of my practice half of the patients were so badly fed that at 3 and 6 months of age they were not much above birth weight. Rickets, with its resulting deformities, was universal. Summer diarrhea doubled infant mortality. Acute infections were not well diagnosed or treated.

The very rapid improvement in health conditions and reduction of mortality has been due to the education of pediatricians and their subsequent work. These specially trained physicians worked for the welfare of children: they crusaded for clean milk and pure food: they taught mothers, nurses, and general practitioners proper care and feeding of infants and children: they organized the service for newborn and sick children in the hospitals.

In each community where a good pediatrician was located, hundreds benefitted for every child he saw as a private patient. The steady progress which has made the children of the United States the healthiest in the world has been the work of these pioneers and missionaries, working as individuals and through their voluntary associations. During this time they have contributed more to the advance of medicine than all other countries of the world combined.

Would this have been true if a paternalistic government had undertaken to furnish all children with health care, as education is provided by our government? I cannot believe that it would. I fear interference with our present freedom of enterprise and endeavor. I believe the most productive expenditure of public funds would be to assist young graduates during years of internship and residencies. Not until more pediatricians are educated will we have better care for more children.

The organization of Region V, comprising the Latin-American countries, is a promising step in our advancement. As you know we were forced to give up plans for a Pan-American congress in 1948. We hope that the Washington meeting arranged by Dr. Hurtado for the members of this region, will speed up its growth and lead to a closer union of the pediatricians of the Western Hemisphere.

I was present at the birth of the Academy, when about a dozen of us met at the home of Dr. James Rosenfeld, during an A.M.A. convention in Portland. We decided the time had come to create a national society of pediatricians. That night, the name "Academy of Pediatrics" was chosen at the suggestion of Dr. Isaac Abt. Dr. Grulee was suggested as secretary, and each of us made a list of ten, who were invited to become charter members. It was my privilege to serve on the first executive board as regional chairman. Now, in my later years, I have come back into its inner councils. I find it has attained maturity. It is a strong, vigorous, "going" concern; the finest

ideals of service have governed its leaders. It has made an outstanding contribution to the development of pediatrics. I am very proud to have had a small place in its history.

In reviewing the growth and development of the Academy, I wish to pay tribute to the man who has made the greatest contribution to its success. From the beginning, our secretary, Dr. Grulee, has been the mainspring. Without his assistance and advice, the elected officers would have trod a difficult and uncertain road during their brief terms of office. His conservative yet constructive influence in the Executive Board's direction of affairs, has been a great factor in avoiding mistakes and furthering worth-while undertakings.

There is a project under consideration for the erection of a building to house a library and museum and perhaps the Academy offices. As many of you know, Dr. Grulee has a very large and complete private pediatric library, which he offers to give us. I sincerely hope, that means may be found for the proposed building. No matter what name it is given, to me, it will be a monument to the lifework of Dr. Clifford Grulee.

DEFICITS IN DIARRHEA

JAMES L. GAMBLE, M.D.
BOSTON, MASS.

THIS paper discusses briefly the development in diarrheal disease of deficits of body water and electrolyte on the one hand and of energy stores on the other, with the purpose of defining features of difference which have relevance to parenteral fluid therapy.

Since water and the electrolytes are not destroyed within the body, they will serve the body as long as the body can hold on to them. This is not the case for the oxidizable food substances which sustain the energy metabolism. It is their destiny to be destroyed; they serve the body only once. Reductions of uptake of water and electrolytes from the gastrointestinal tract will result from increased outgo in the stools and also from lowering of the infant's ability to accept food. The usual intake of water and electrolytes by an infant provides a very large surplus over obligatory outgo in the urine. So we can have large reductions of uptake from the gastro-intestinal tract which will be covered by corresponding limitation of removal of water and electrolytes by the kidney. When, however, the limit of renal conservation is overpassed, deficits will develop with dangerous rapidity. The infant's food provides only the small surplus of oxidizable substances, above the requirement for energy expenditure, which is needed for growth. Even a small reduction of uptake of these substances will, therefore, cause progressive depletion of the energy stores of the body. In other words, in contrast with water and electrolytes, there is no adjustment which will offset reduction of calory uptake. These are quite simple and evident physiologic propositions. The purpose of the following data is to give them quantitative illustration.

The data in Chart 1 are borrowed from a recent unpublished study of water balance in infants by Pratt and Bienvenu (personal communication). The first diagram presents the values found for the components of the water exchange of a 3 kg. infant receiving a food intake composed of a usual dilution of evaporated milk. The intake of water is shown on the left side of the diagram together with the water produced within the body by oxidation of the food substances. On the outgo side we have a relatively small loss of water in the stools and the water which leaves the body by way of the lungs and skin, the so-called insensible water loss, which has an approximately stationary value. Regulation of the remainder of water outgo so as to provide the small positive balance required for growth, shown at the top of the diagram, is performed by the kidney. This water is much more than the kidney needs for excretion of the daily quantity of substances claiming removal in the urine. The measurements recorded in the next diagram of the chart are from a period during which the infant was given

Borden Award, Fifteenth Annual Meeting of the American Academy of Pediatrics, Pittsburgh, Pa., Feb. 24-27, 1947.

undiluted condensed milk. A normal water balance was found in the presence of reduction of water intake to about one-fourth the usual quantity. There were small reductions of insensible water loss and of water in the stools, but, as the diagrams make quite clear, the large adjustment which preserves water balance is limitation of water outgo by the kidney; urine water is reduced to about one-eighth the quantity found for a usual water intake. These data serve to show the very large water surplus which a usual food intake provides and the extensive conservation of water which can be gained by regulation of outgo in the urine.

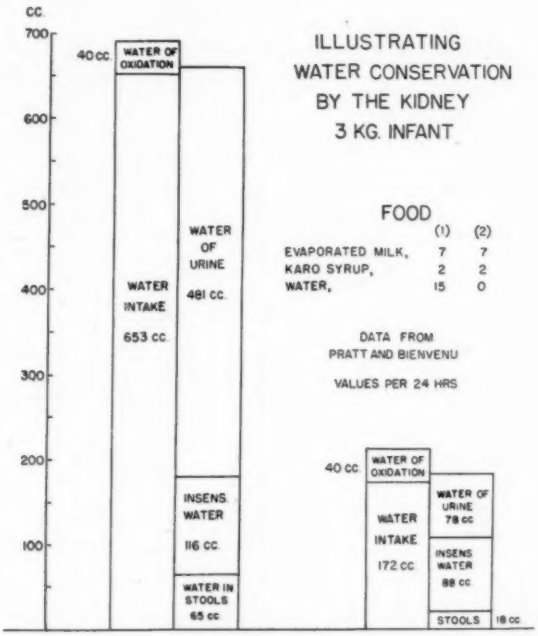


Chart 1.

The diagrams in Chart 2 are constructed from values taken as average for a 7 kg. infant. The first one defines the components of the water exchange with a usual food intake. The small water loss in the stools is placed at the top of the outgo column and the fixed value for the insensible water loss at the bottom. In between is the water removed by the kidney to the extent which provides the small water gain to the body which growth requires. In the next diagram, water expenditure by the kidney has been reduced to its minimal value with the purpose of measuring the extent to which water may be lost in the stools in the presence of a usual intake without disturbing water balance. Very rarely does diarrhea produce a stool volume as large as this. According to the classical study of Holt, Courtney, and Fales, the average value for daily loss of water in the stools of severe diarrhea may be taken

as 300 c.c. As shown by the broken line across the diagram, a stool volume of 300 c.c. will not disturb water balance until intake falls below about two-thirds of its usual value.

The other pair of diagrams have to do with sodium. Sodium and its companion extracellular fluid ion, chloride, are particularly exposed to loss in diarrheal stools because they are the two large components of the gastro-intestinal secretions. The first diagram displays the enormous surplus of sodium which the infant's food provides in relation to the small daily gain to the body which growth requires. Under normal circumstances, only the small bit of sodium shown at the top of the outgo column is lost in the stools, and so the huge surplus from intake has to be carried into urine. The kidney can limit outgo in the urine to the very small quantity shown in the next diagram.

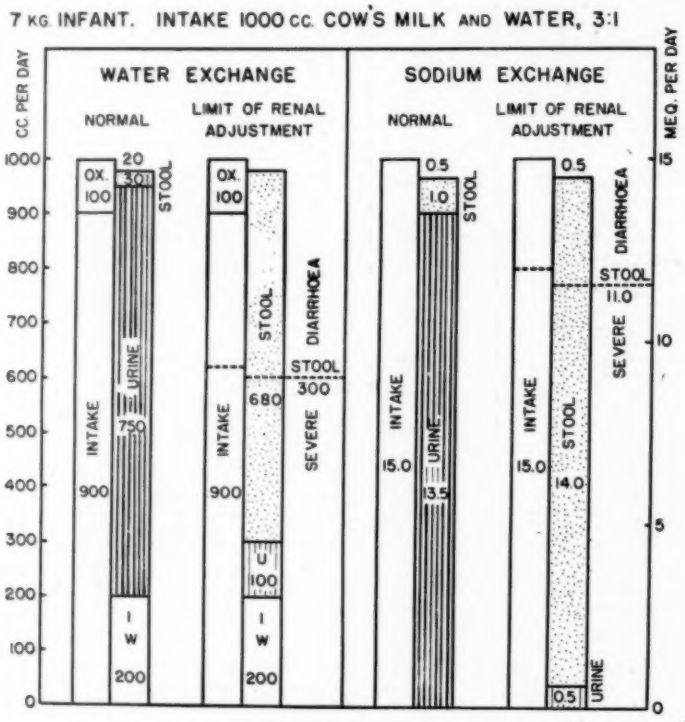


Chart 2.

According to the small values for retention and obligatory outgo in urine shown in the diagram, more than 90 per cent of sodium intake can be lost in the stools without causing deficit. The position of sodium balance is not, however, so secure as these data suggest, for the reason that the loss of sodium in diarrheal stools is relatively somewhat larger than the loss of water.

Using the average value found by Holt, Courtney, and Fales* for sodium in the stools of severe diarrhea, the permissible reduction of intake is found to be somewhat less than for water.

So, according to these diagrams, owing to the kidney's ability to extensively conserve water and sodium, balance may be preserved in severe diarrhea, even when there is considerable reduction of intake. It is evident from the diagrams that, with further reductions of intake, deficits will develop. At the outset of acute severe diarrhea there is extensive, often complete, refusal of food, followed by gradual recovery of intake tolerance. It is evident from the chart that, for a given degree of diarrhea, the requirement for parenteral provision of water and electrolyte will be determined by the extent of reduction of intake.

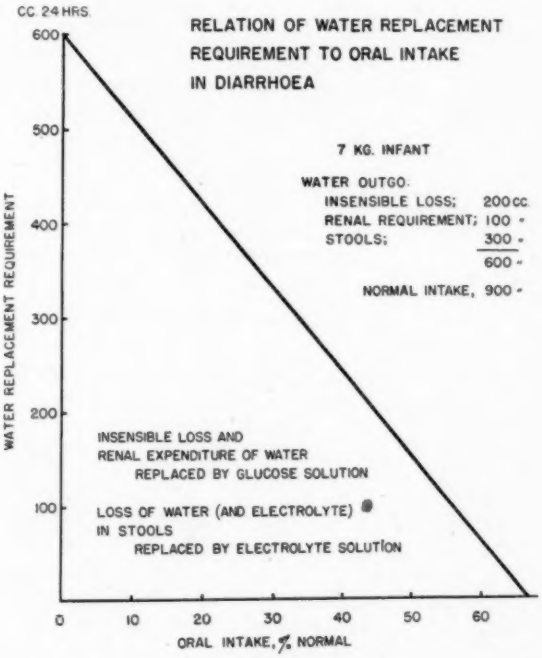


Chart 3.

This is shown in Chart 3, in terms of the water requirement for a 7 kg. infant with a daily stool volume of 300 c.c. and an obligatory water expenditure of 300 c.c. by way of the lungs, skin, and kidneys. So that, with no oral intake, replacement of 600 c.c. of water will be required parenterally. It may be noted here that glucose solution should be used to cover the physiologic expenditures of water, and electrolyte solution to replace the pathologic loss of body water and electrolyte in the stools. When intake is built up to 65 per cent of the usual quantity, this hypothetical infant will not require water parenterally.

*Holt, L. E., Courtney, A. M., and Fales, H. L.: Am. J. Dis. Child. 9: 213, 1915.

This chart is intended to illustrate the relation of current water deficit to intake. It makes no allowance for body fluid deficit incurred before institution of treatment. This deficit must, of course, be estimated for the individual patient and replaced by additional electrolyte solution.

Chart 4 is intended to display the main features of difference between water deficit and calory deficit in relation to survival. This is a much more venturesome fantasy from the armchair. The data should be accepted with several grains of electrolyte. We have again our standard 7 kg. infant who voids with preposterous precision a daily stool of 300 c.c. and receives along the abscissa a declining food intake. Estimations of days of survival, based on rates of expenditure of body fat and of body water, are recorded on the ordinate.

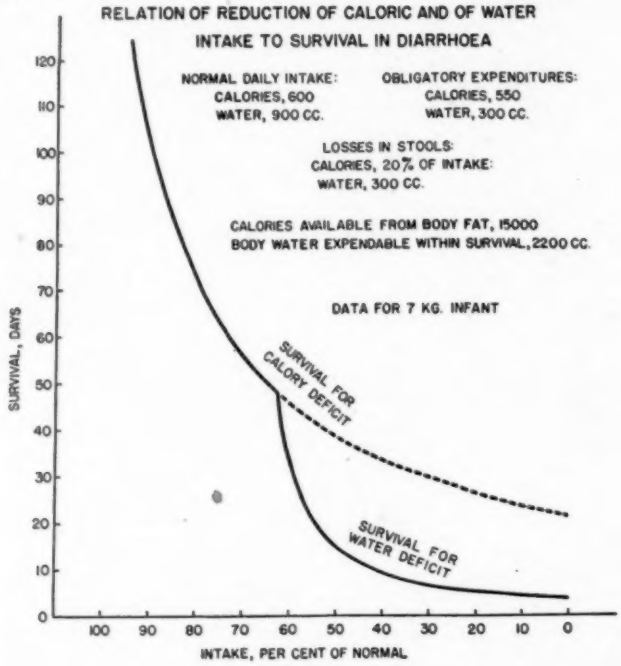


Chart 4.

The infant is assumed to have been well nourished at the outset of diarrhea and to have had fat on deposit in his body to the value of 15,000 calories. It is also assumed that the daily loss of calories in the stools is 20 per cent of the intake. The quantity of body water expendable within survival is taken as 2,200 c.c.* Estimation of daily deficit at a given reduction of intake is derived from the values on the chart for normal intake, obligatory expenditure, and loss in the stools. Survival is then estimated by dividing the calories

*Estimated on the basis of maximal losses within survival of 30 per cent of intracellular and 60 per cent of extracellular body water.

available from body fat and expendable body water, by the deficits found respectively for energy and water.

As has already been considered, loss of the oxidizable food substances from a usual food intake produces energy deficit, and this deficit will obviously be increased by reduction of the food intake. Energy deficit, then, begins at the outset of diarrhea, but, according to the preceding chart, water deficit will not begin to develop until food intake has been considerably reduced. And so, as shown by the chart, survival in relation to reduction of intake is at first governed by energy deficit. On the basis of a loss of 20 per cent of energy intake in the stools, survival expectancy for a 10 per cent reduction of intake is, according to the chart, 100 days, and falls to fifty days for a 30 per cent reduction. With further reduction of intake, the limit of renal defense of water balance is overpassed and water deficit takes over command and brings survival rapidly down to the desperately narrow margin of three or four days for the situation of complete intake intolerance.

For the long-lasting watery diarrheas produced by persistent parenteral infection and by other causes, the situation is described by the first part of the chart. Limitation of food intake is usually not extensive, so that dehydration is not often a feature of these diarrheas, even when the stools are very large. The infant approaches the edge of existence gradually by way of calory deficit.

An outstanding feature of acute severe diarrhea is extensive, often complete, failure of food acceptance by the infant. By energetic provision of water and electrolytes parenterally we can sustain the body fluids in this situation and bring survival expectancy back to the limit imposed by calory deficit as shown by the broken line on the chart. The broken line tells us that the interval of time within which this infant must be carried through a severe episode of acute diarrhea, by sustaining the body fluids until food intolerance abates and then rebuilding the food intake, is twenty to thirty days.* Ordinarily, this can be accomplished well within the period of grace, so that we do not have to worry about the progress of calory deficit toward the survival limit. But, unfortunately, we encounter many instances of severe diarrhea, with more or less extensive reduction of intake tolerance, which run a protracted course measured in weeks rather than days. If this chart is anywhere near the mark as an estimation of this situation, the requirement for provision of calories parenterally must be recognized.

How to do this is the most urgent problem in the treatment of diarrhea. More glucose can be provided by using a 10 per cent solution instead of the usual isotonic 5 per cent solution. Infusion of higher concentrations of glucose is, on several counts, undesirable. It would also be desirable to reduce the loss of body protein which is incidental to a sub-energy maintenance intake, which probably limits survival more narrowly than does depletion of the fat stores of the body. Unfortunately, unless the energy requirement is completely covered, the greater part of protein provided parenterally in the form

*The small contribution to energy incidentally provided by the glucose solution given to sustain the water exchange should extend survival for calory deficit slightly beyond the broken line.

of hydrolysates will be oxidized for energy. It is possible to provide a full calory intake by continuous, or almost continuous, infusion of 10 per cent glucose solution. This procedure requires, besides technical experience, constant surveillance by especially skilled nurses, and so is not widely available. It also requires a volume of water which is far beyond the physiologic need.

The great desideratum would seem to be fat in such form that it can be given parenterally, and it is to be hoped that current attempts to produce a preparation of fat which will serve this end will go forward successfully.

RICKETTSIAL DISEASES OF CHILDHOOD

A Clinical Pathologic Study of Tick Typhus, "Rocky Mountain Spotted Fever," and Murine Typhus, "Endemic Typhus"

J. Cyril Peterson, M.D., James C. Overall, M.D., and John L. Shapiro, M.D.
Nashville, Tenn.

ROCKY Mountain spotted fever and murine or endemic typhus are the important proved rickettsial diseases of children in this country. In recent years, there has been a marked increase in the known area of endemic Rocky Mountain spotted fever. There has also been a marked spread of the areas of endemic infection and a marked increase in the number of cases of murine typhus fever. A number of brilliant epidemiologic studies have appeared, which aid in a definition of the over-all problem of rickettsial disease, but there is a paucity of material concerning the clinical manifestatons of Rocky Mountain spotted fever in children and an almost complete absence of clinical studies of murine typhus in children.

In the past fifteen years we have had an opportunity to study twenty-six cases of Rocky Mountain spotted fever, with seven autopsies, and, since 1942, fifteen cases of murine typhus in children. This clinical material, while small in amount, has been studied systematically* and should enable us to add substantially to the clinical descriptions and to information concerning pathologic physiology of the diseases.

The recent introduction of a satisfactory therapeutic agent for the treatment of rickettsial infections makes such a study timely.

The term "Rocky Mountain spotted fever" has lost most of its significance. The disease is no longer so geographically limited. The inclusion of Sao Paulo fever and Colombian spotted fever with Rocky Mountain spotted fever extends the geographic limits of this disease within the western hemisphere. The term "tick typhus" would seem to be a simpler and a more significant designation for the disease. The word typhus (Greek: *typhos*, meaning cloudy or stuporous) is certainly a descriptive term, more appropriate for this disease than for the milder murine typhus. And, as far as has been determined, some species of tick is invariably responsible for the transmission of the disease. The term tick typhus will be used throughout the remainder of the paper, not only because we think it a more appropriate term, but also because of its desirable brevity.

The endemic typhus fever in this country has been designated by a number of terms, and of these, Brill's disease has real merit from the viewpoint of priority but eponymic nomenclature of disease suffers from descriptive poverty.

From the Departments of Pediatrics and Pathology, Vanderbilt University School of Medicine, Nashville.

Presented before the Fifteenth Annual Meeting of the American Academy of Pediatrics, Pittsburgh, Pa., Feb. 24-27, 1947.

*The study of these cases was initiated under the guidance of Dr. Katharine Dodd and Dr. Ann Minot. They were cognizant of the significance and importance of the endothelial lesions of the capillary bed and of their relationship to many of the manifestations of these diseases.

Since this typhus has been established as an entity, it would seem best to use a name with more significance than the term endemic, particularly as it is not a disease limited to this country. The term murine typhus, because of its epidemiologic connotation, seems superior to either Brill's disease or endemic typhus. It might even be desirable to call it rat typhus if that would focus public attention upon the necessity of getting rid of rat populations.

TICK TYPHUS

Tick typhus is an acute, self-limited, infectious disease of variable severity. The etiologic agent is the *Rickettsia rickettsii*, an obligate intracellular parasite of several species of ticks and of rodents and possibly other mammals. The rickettsia is passed hereditarily from one generation of ticks to another and does not seem to have a deleterious effect upon this host. It is transmitted to man by the bite of the adult tick and occasionally by the bite of nymphal forms. The crushed tick may also serve as a source of infection. The western wood tick, *Dermacentor andersoni*, and the eastern dog tick, *Dermacentor variabilis*, are the principal vectors, but other ticks, *Dermacentor occidentalis*, *Amblyomma americanum*, *Haemophysalis leporis-palustris*, and *Amblyomma cajennense* have been incriminated in the transmission of the disease.

It is fifty years since Woods,[1] an army surgeon, first called to our attention the fact that physicians practicing in southern Idaho had recognized a new disease, a "spotted fever" which was distinguishable from meningococcemia and other known purpuric fevers. This obscure report was quickly followed by the clinical reports of Maxey[2] describing the mild form of the disease as seen in the Snake River Valley in Idaho, and of McCullough[3] describing the severe form of the disease as seen in the Bitter Root Valley in Montana.

These studies were in turn followed by a number of systematic investigations[4-6] into the epidemiology and etiology of the disease which culminated in the work of Ricketts[7] who showed that the disease was caused by a parasite of the wood tick, *D. andersoni*, hereditarily passed from one generation of ticks to another.

Wolbach,[8] in 1919, completely reviewed the previously accumulated information concerning tick typhus, elaborated upon most of the important pathologic features of the disease, and more significantly described the presence of the *R. rickettsii* in the endothelial and smooth muscle cells of the vascular system.

In 1931 Badger, Dyer, and Rumreich[9, 10] demonstrated that tick typhus was not limited to the mountainous section of western United States, but was endemic in the eastern part of the country and that the dog tick, *D. variabilis*, was probably responsible for the transmission of the disease in the eastern United States. They further showed that tick typhus in eastern United States had been confused with murine typhus fever.

Since these studies, there has been widespread recognition of tick typhus throughout the country, cases having been reported from all states but a few in New England. In the five years from 1940 through 1944, cases were reported from every state except Main, Vermont, Rhode Island, and Kansas. Certain

foci of relatively high prevalence are recognized. Chart 1 shows the summary of reported cases in the United States for the years 1940 to 1944, inclusive. Fig. 1 shows the numerical prevalence of reported cases in the states for the same period. From this illustration it is apparent that while the major foci of the disease are in the upper South Atlantic states and in the northwestern mountain area, the disease is endemic throughout the United States.

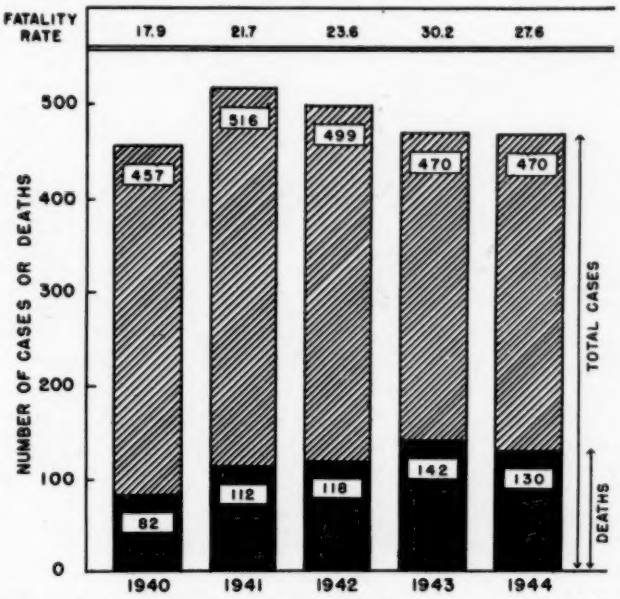


Chart 1.—Number of cases and deaths from tick typhus in the United States from 1940 through 1944.

While it is strongly suspected that tick typhus was occurring in the East prior to 1931, it is not probable that this disease has long been endemic there. It would seem improbable that a disease would be immediately recognized as being different in the West and would remain completely hidden in the East. Nor can this be entirely attributed to confusion with murine typhus, as that disease was not and is not common in many areas where tick typhus has been recognized only in recent years. It is true that most of our patients were seen by physicians and were not correctly diagnosed before they came to the hospital, but some were recognized and many were sent for diagnosis because the physician realized that they were different from infections with which he was familiar.

In Tennessee the study of Litterer[11] makes it seem possible if not probable that the infection was an importation from Montana. Wolbach[8] has pointed out that the disease is not likely to be transported from one area to another by the rodents which serve as reservoir hosts but that it might be transported by larger mammals carrying the tick from one area to another. The establishment of the disease in an area depends upon the presence of satisfactory conditions

for the propagation of ticks susceptible to infection, susceptible rodents to spread it locally, and larger mammals to carry the infected ticks to different localities.

In the eastern states the infection is transmitted by and is endemic in dog ticks. These ticks may be carried from place to place by dogs and other larger mammals, thereby providing excellent means for the spread of parasitized ticks and also for the spread of the infection to rabbits, the cottontail[12] seemingly being an important factor in the maintenance of the disease.

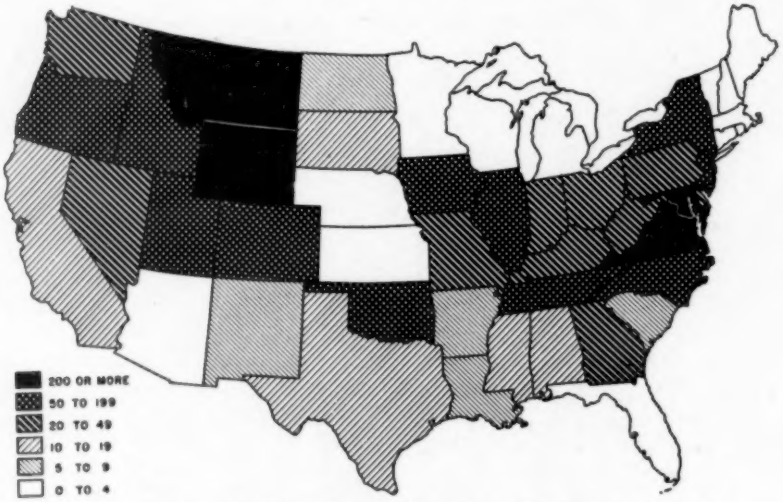


Fig. 1.—Geographic distribution of tick typhus (1940 through 1944).

Tick typhus tends to be a disease of spring and early summer in the West. There the principal vector, the wood tick *D. andersoni*, tends to become dormant with the drought and heat of summer. In the East the cases have a somewhat different seasonal pattern, the principal vector, the dog tick, remains active for a much longer period, and infection is possible the year round but occurs principally in the summer. Twenty-one of our twenty-six patients were seen in the months of June, July, and August. The seasonal distribution is shown in the following table.

TABLE I. SEASONAL DISTRIBUTION OF REPORTED CASES OF TICK TYPHUS

	JAN.	FEB.	MAR.	APR.	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.
U. S., 1940-1944*	12	8	35	166	424	493	529	440	181	66	29	16
Our cases	0	0	0	2	2	5	11	5	2	0	0	0

*United States Public Health Reports supplements 166, 172, 184, 182, 190. The Notifiable Diseases.

The epidemiologic study of Topping[13] explained certain significant differences which have been noted between the disease in the West and in the East. The higher mortality in the West was found to be due almost wholly to the fact that 50 per cent of all cases there occurred in adults past 40 years of age,

while in the East 47 per cent of the cases occurred in children under 15 years of age. The cases of comparable age distribution show the fatality rates to be quite similar. He showed that the disease is more common in the male in both sections but that the difference is much less in the East, and in children females are affected almost as frequently as males.

While there is little difference in the general severity of the disease when the country as a whole is considered, local differences have been noted since the earliest studies[1, 2] and different strains of the rickettsia produce disease of differing severity in experimental animals.

Pathology.—The pathologic lesions of tick typhus provide an excellent background for the interpretation of the clinical manifestations.

A number of excellent studies on the pathology of tick typhus by Anderson,[5] LeCount,[14] Wolbach,[8] Harris,[15] Lillie,[16] Allan and Spitz,[17] and others, have described all of the important pathologic lesions. Many of these studies, however, have been made with scant reference to the clinical manifestations, and in advance of some clinical interpretations. They have consequently emphasized the pathologic histology of the disease in a disproportionate manner.

A brief review of the changes encountered in our cases will serve to orient the reader to our interpretations.

Generally speaking, the most obvious lesion and the one which serves as the most satisfactory locus for the demonstration of rickettsias in tick typhus is the acute arteritis. This lesion has been adequately described by the authors in the foregoing citations. Notwithstanding the attention which has been devoted to this lesion and regardless of its value in the diagnosis of tick typhus, it is not the most important anatomic change in the pathogenesis of the disease. This is most easily appreciated when one considers that the arterial lesions are more prominent in the skin and in the testis than any other organ or tissue and it is obvious that the arterial lesions in these locations can have no fatal consequence, nor could they explain many of the clinical features of the nonfatal disease. If, then, the arterial lesion is responsible for neither the fatal outcome nor the principal clinical features of the disease, some other lesion must be incriminated. Although the lesion to be described has been previously noted, it has been more or less neglected because it is much less spectacular than the arterial lesion. It is much more widely disseminated, however, and is much more significant in explaining the clinical features of the disease. This lesion, a generalized capillary injury, is uniformly encountered in all cases studied, and it adequately explains all of the significant features of the disease.

While capillary damage is found in all of the tissues and organs of the body, it is nevertheless more easily demonstrable and more significant in certain organs. Generally speaking, from the clinical point of view, the principal cause of death seems to lie in the disturbed function of the cardiorespiratory systems. From the pathologic point of view, there is ample evidence to indicate that each of these systems is seriously damaged. The lesion in each is essentially similar and any difference can be explained by the anatomic structure of the

tissue involved. The essential lesion is an alteration in the capillary bed which is characterized by edema, the accumulation of mononuclear, inflammatory cells, and occasionally by fibrin thrombi in the capillaries.

In the heart this is associated with focal destruction of myocardial fibers and an accompanying mononuclear leucocytic infiltration. These changes are shown in Fig. 2.

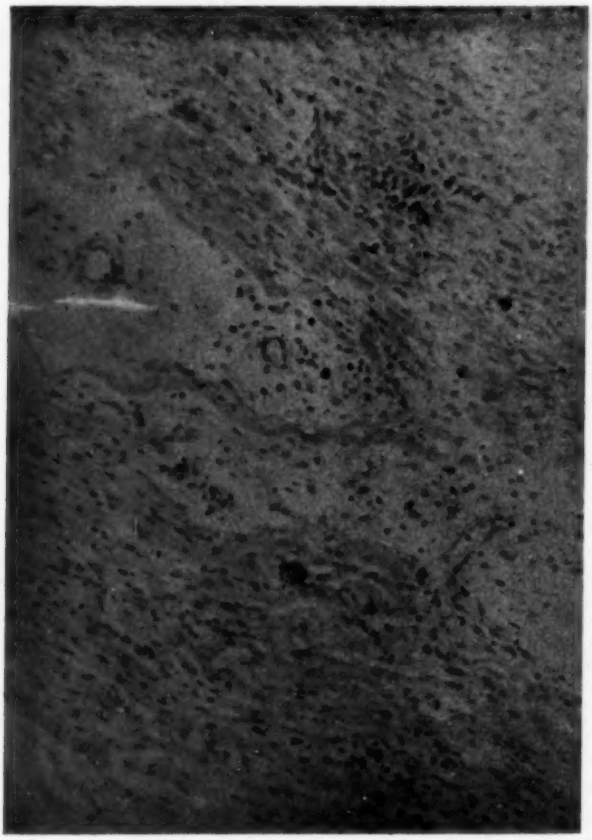


Fig. 2.—The myocardial changes resulting from tick typhus.

In the lungs, the process is recognized as acute interstitial pneumonia, the principal feature of which is serous exudate in the alveolar spaces; but in addition to this one finds mononuclear infiltration of the alveolar walls and, to a lesser extent, the spaces.

The concurrence of these lesions in the heart and in the lungs is so significant that it should allow one to make a tentative pathologic diagnosis of rickettsial disease of the severer type, either scrub typhus or tick typhus. It is

significant and important that the arterial lesions in the heart and in the lungs are very difficult to find. One also finds petechial hemorrhages similar to those which are found throughout the body, but these are of no particular importance.

While alterations in the liver are not as prominent or as important as are those in the heart and lungs, they are, nevertheless, of real significance. The anatomic lesion is characterized by the same capillary damage which has been described before. The localization of the lesion is predominantly in the periphery of the lobule, but there is edema throughout the lobule. Though the intrinsic lesion in the liver is not very impressive, it assumes greater importance when considered in the light of the known function of the liver in the production of plasma protein and especially in the face of the loss of plasma protein because of the widespread capillary damage.

Although Harris has described microscopic infarcts, presumably on the basis of arterial lesions in the brain, we have been unable to find these in any other case. Nevertheless, one finds in the brain the same altered capillary permeability, as indicated by edema and hemorrhage, and it is thought that these can adequately explain the central nervous system manifestations of the disease. These lesions themselves, however, are not usually of sufficient intensity to have any important relationship to the fatal outcome of the disease.

The lesions in the alimentary tract are relatively insignificant in themselves, but it is probable that they interfere with normal alimentation. This may be of especial importance in the digestion and absorption of proteins. Such a disturbance contributes another facet to the complex picture of plasma protein depletion, which is so characteristic in tick typhus.

The lesions in the kidney do not appear to be very significant, but they can adequately explain the mild albuminuria and retention of nonprotein nitrogen encountered in the disease. They are characterized by increased cellularity of the glomeruli and by focal accumulation of inflammatory cells around the thrombosed capillaries of the corticomedullary zone.

The classical cutaneous manifestations are undoubtedly due to arterial lesions, but the widespread edema of the skin and of the body tissues generally must be explained on another basis, and here again the alteration in the capillary permeability is of greatest importance. Anatomic evidence of this damage is detectable in the skin and it resembles in all respects the lesions described in other organs.

While the organs and tissues already discussed appear to be those most significantly and seriously injured, the lesions are by no means restricted to these, for the adrenals, testis, pancreas, and almost every other organ and tissue is similarly involved.

There is one other lesion which at the moment is only of academic interest. This is the characteristic phagocytosis of red blood cells, especially by the reticuloendothedial cells of liver and spleen, but in other organs as well. This erythrophagia is of such a degree that it might well contribute to the anemia which is encountered in some of these patients.

Clinical Manifestations.—The onset of the disease is usually abrupt after an incubation period of from two to thirteen days. In two persons purposefully

infected by McCalla[18] by a tick taken from a person with the disease, the incubation period was three days in one and nine days in the other. In our material the incubation period varied from three to ten days in the fourteen patients where a definite bite or contact could be determined. In two patients there was no definite contact with ticks; in two others no ticks were removed but bites were noted the day before the onset; in four patients the ticks were still attached when they were first seen at the hospital. One patient was unsuspected and the question of tick bite was never raised; three were associated with simple handling of the ticks in removing them from dogs (in two of these the tick was squeezed between the fingernails). In one instance the time of removal of the tick was not recalled and in one instance the only known contact was three weeks before the onset. The incubation period in the fourteen known intervals is shown in Table II.

TABLE II. INCUBATION PERIOD IN TICK TYPHUS

Day after bite	3	4	5	6	7	8	9	10
No. cases	4	1	2	1	3	1	-	3

The first complaint in almost every case was severe, unlocalized headache; this persisted as the outstanding symptom until the patients became too stuporous to complain. Aching pains were noted in twelve instances but they were never referred directly to the joints and were often generalized. Anorexia with refusal of almost all foods was usual. There was occasional abdominal discomfort. There was vomiting at the onset in six instances and diarrhea twice as the only other gastrointestinal manifestations. In one-fourth of the patients there were chilly sensations but none of them had frank shaking chills.

The rash was the symptom most likely to alarm the parents and appeared first as a few scattered red macules. The rash usually appeared on the extremities first but this was far from being regular. In the most severe cases the rash began to show petechial hemorrhage into the macule very early but in the milder cases the purpuric quality of the rash first appeared after a period of several days to as long as a week. The rash appeared in less than forty-eight hours after the onset in thirteen instances, in four during the first twenty-four hours, and in several others very early on the second day.

The time of the appearance of the rash and whether it appeared first on the trunk or on the extremities in twenty-six patients seen during the active disease is shown in Table III.

TABLE III. THE TIME AND SITE OF FIRST APPEARANCE OF THE RASH IN TICK TYPHUS

WHERE RASH WAS FIRST SEEN	DAYS OF ILLNESS						TOTAL
	1	2	3	4	5	6	
Extremities	4	7	1	3	1	0	16
Trunk	0	2	2	3	1	1	9
Total	4	9	3	6	2	1	25*

*In the one Negro patient, the rash was not noted prior to admission.

Another pertinent complaint of these patients, especially those seen in the second week of their illness, was stiffness of the neck and back. This was likely

to have been overlooked in the seriously ill, stuporous patient even if spinal fluid showed marked changes from meningeal inflammation. The stiffness of the back and neck was seen, however, in patients who did not have spinal fluid changes on admission and was a prominent symptom in some who died early in the disease.

Several of our patients were brought in with the complaint of swelling, generalized edema, and in one instance this was the chief complaint in that the patient was unable to open his eyes.

Symptoms referable to the respiratory tract were not common, though two patients had signs of pneumonia at the time of admission.

Many patients were treated for several days with quinine in the belief that they had malaria. This was invariably in the stage before the appearance of the rash. Typhoid fever did not enter into the early errors in diagnosis.

As all except one patient had a rash when brought to the hospital, it is not surprising that almost all were correctly diagnosed at admission. The exceptions were the first patient, who was seen in 1931, only four months after the announcement of Badger and Rumreich that the tick typhus had been found in patients in the eastern United States; and a patient without a rash but with an infected foot wound and meningismus which led everyone to suspect atypical tetanus. His rash appeared late on the day of admission, the fifth of the disease, and he died the following morning. The correct diagnosis was made only when the tissues were examined microscopically.

The physical findings at the end of the first week and early in the second week, when the patients came to the hospital, were very typical but were quite limited. On inspection they were all obviously quite ill.

The milder cases were so apathetic that one had to be forceful to arouse their attention and the more severe cases were in semicoma to complete coma. Their facies, which are well illustrated by the photographs, are typical enough to be diagnostic. They show a general clouding of the sensorium just short of that usually seen in acute encephalitis. This finding is undoubtedly due to the widespread involvement of the cerebral vascular system. It is present as early in the disease as the appearance of the rash, in some instances before the rash is apparent, and reaches its maximum degree at the end of the second week or during the third week in the more protracted cases. In the least severely ill patients the typhus state persists only until the fever begins to break but in the most severely ill it may persist well into convalescence. Undoubtedly some patients never recover completely from this encephalopathy. The last patient of our experience, 120 days after the onset, still has marked encephalopathy, central blindness, and central deafness, together with slight but definite hemiparesis. She has just learned to sit up again and has not regained any power of speech. In Fig. 3 is shown the facies of a patient with severe tick typhus four days after his temperature had returned to normal. Three weeks later he was talking with some slight degree of spontaneity but was still mildly ataxic. These severe degrees of encephalopathy are fortunately exceptional. It is interesting that there were convulsive seizures in only one of our patients in spite of the

fact that meningoencephalitis was commonly demonstrated both clinically and by spinal fluid changes (see below).

All of our patients showed a slight-to-moderate, generalized edema. Their faces were moon-shaped and the folds about the eyes, wrists, and ankles were obliterated. In the very mildest cases findings were minimal; in the moderate and severe cases they were quite obvious, and in two instances the eyes were swollen shut at some time in the course. This edema appeared as early in the disease as we saw the patients. This is in contrast to five adults whom we have seen with the disease; they, with one exception, were free from easily perceptible

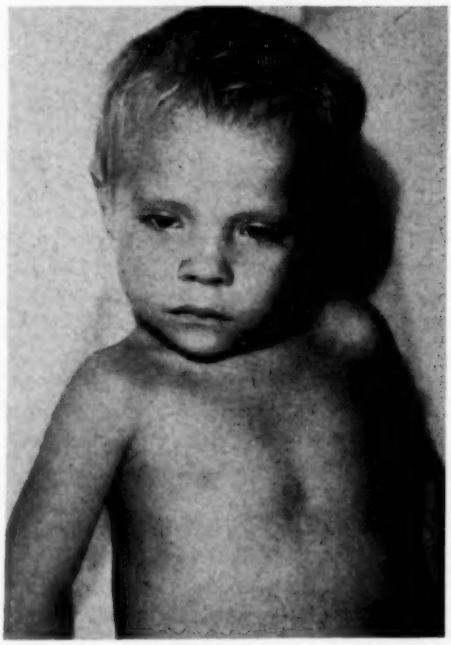


Fig. 3.—Encephalopathic facies and skin pigmentation seen in patients with tick typhus.

edema. The edema is not easily pitted. As seen in the photographs it is generalized and involves both the cutaneous and subcutaneous tissues. This edema fluid is rich in protein, as is easily demonstrated in pathologic sections, and is, no doubt, due to the generalized damage to capillary endothelium. That the loss of protein in this manner is important is shown by the fact that the plasma proteins were regularly reduced but not sufficiently to have been a factor in the development of the edema. In some instances the edema may also have been in part due to cardiac failure but in the main it was the result of the capillary damage.

The rash was the principal general physical finding. Its character is well illustrated in the colored photographs.* The rash appears first as discrete red

*The authors were able to publish this plate through the courtesy and generosity of Wyeth Incorporated, who also supplied the para-aminobenzoic acid used in the treatment of some of the patients.

Fig. 1—TICK TYPHUS
The exanthem, facies and generalized edema, especially of the eyelids, as seen in the first week.

Fig. 2—TICK TYPHUS
The exanthem during the second week, with purpuric qualities.

macules which blanch incompletely on pressure. They may appear first on any part but most frequently on the extremities (see Table III). Regardless of where the rash first appears, it soon becomes much more marked on the extremities and involves the palms of the hands and soles of the feet. In all but the mildest cases, the rash, after a period of two to three days, begins to show purpuric manifestations, becomes more intensely red, and fades little if any on pressure. The rash may show petechial hemorrhages or even become wholly purpuric in character. In the most severe cases the petechiae are present in the lesions from the beginning. These are difficult at times to differentiate from the petechiae of meningococcemia. As a rule, however, there is more associated erythema with the lesions of tick typhus.

The rash persists until the patient begins to show signs of improvement, but may begin to fade several days before the lysis of the fever begins. The fading rash leaves a distinct pigmentation of the skill, most marked on the patients who had the severest purpuric manifestations. The character of this pigmentation is apparent in Fig. 3. In the severely purpuric patients the pigmentation may persist for ten days to three weeks before disappearing.

In addition to the above general findings, several other physical changes occur. In all but one of our patients there was a tachycardia higher than one would expect from the observed fever alone. Pulse rates of 140 to 160 were seen, with temperatures of 102° to 104° F. This tachycardia was not infrequently associated with poor quality of cardiac sounds and gallop rhythm. Where these findings were marked there was also distention and tenderness of the liver; but we did not demonstrate clearcut signs of pulmonary congestion by physical examination. Chest roentgenograms usually showed considerable increase in the bronchovascular markings and sometimes slight dilatation of the heart. Electrocardiograms much more regularly showed distinct evidence of myocardial damage. There was marked lowering of the voltage. There was slurring of QRS complex, low voltage T_3 curves, and alterations in the S-T segment. These changes are illustrated by the tracings shown in Figs. 4 and 5. In some of our patients the myocardial lesion was an important contributory factor in their death. In association with these cardiac changes there was usually slight hypotension, blood pressure observations were as a rule not greater than 100/50, and 90/50 was a more frequent observation.

The reasons for the cardiac changes are found in the pathologic studies which show a moderate to severe diffuse interstitial myocarditis (see Fig. 2). Also, the extensive lesions of the pulmonary vascular bed serve as important contributing factors in the cardiorespiratory disturbance. In other patients, shock resulting from the loss of fluid and protein from the vascular bed, hemoconcentration, and depletion of the circulating blood served to further augment the anoxemia and to establish a cyclic state of progressive cardiorespiratory failure.

The lungs, while they were affected by an interstitial bronchopneumonia in some of our patients, rarely showed good clinical signs of this change ex-

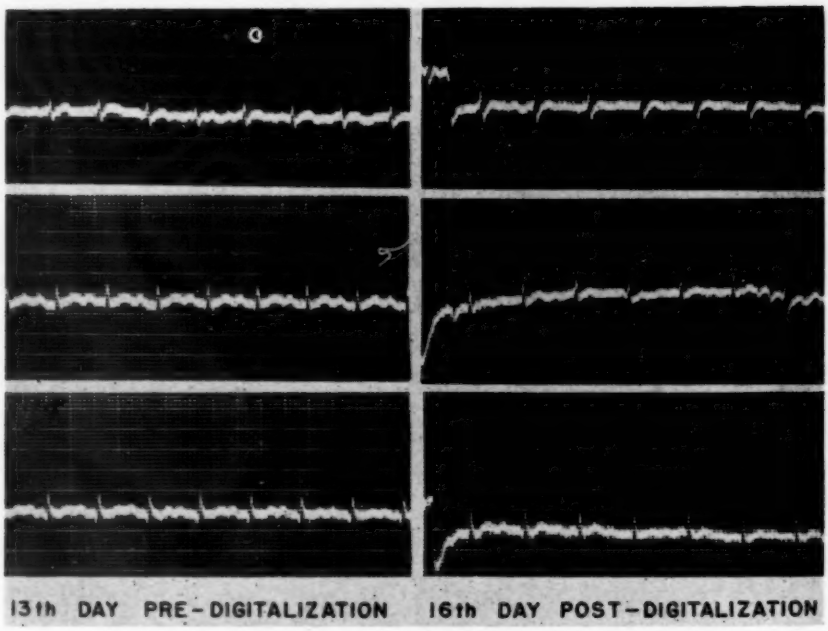


Fig. 4.—Electrocardiographic changes during tick typhus.

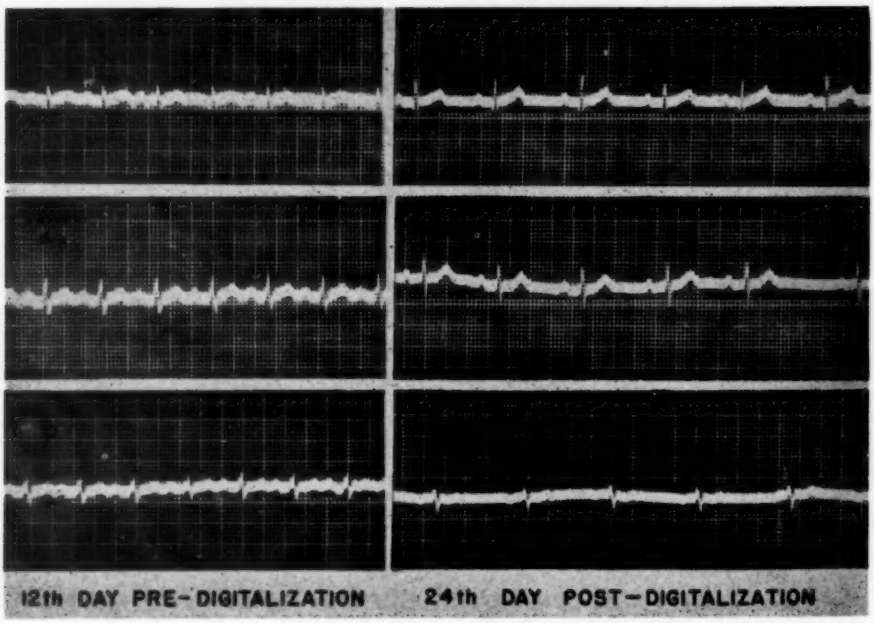


Fig. 5.—Electrocardiographic changes during tick typhus.

cept as a terminal manifestation. Increased and progressive hyperpnea was noted in all of the fatal cases and in some of the patients with severe cases who recovered. Frank decrease in resonance and in the volume of the respiratory murmur with associated râles was found in only two patients at the time of admission; both were fatal cases. The chest roentgenograms as noted above showed only increased bronchovascular markings, and never frank pneumonic consolidation.

The liver as already noted was enlarged in association with myocardial failure but was often not palpable in mild and moderately severe cases. The spleen was palpably enlarged 1.5 to 3 cm. below the costal margin in about half of the patients. There seemed to be no regular explanation for the presence or absence of splenomegaly. This splenic enlargement in the absence of other physical findings in the pre-eruptive phase frequently led to the treatment of the patient for malaria; the quinine, which was usually used, did not modify the course of the infection.

General and local glandular enlargement was noted in about half of our patients, but the significance of this finding in relation to the disease was not apparent.

The freedom from complaints referable to the upper respiratory tract was commented upon above. Only one patient showed catarrhal otitis media and usually the nose and pharynx were clear except for dryness in some instances from the mouth breathing and poor mouth care prior to admission.

Other findings of note were observed in the laboratory studies.

Clinical Pathologic Data.—The urine was, as a rule, normal, though in three or four of our patients there were transiently traces of albumin and a slight increase in red blood cells. These were not more marked than one would have expected to find in any group ill with other fevers of a similar degree of severity.

Some of our patients showed moderate degrees of nonprotein nitrogen retention. Transient elevations of 35 to 50 mg. of nonprotein nitrogen were observed in six of eight patients examined during the fifth to tenth day of the illness. Nine other patients observed after the tenth day showed levels of less than 32 mg. Only two patients showed an elevation of nonprotein nitrogen beyond the tenth day, one was a fatal case with myocardial failure, and the other also had severe myocarditis and cardiac failure. The elevations were greatest in the fatal cases and the three such cases in whom observations were obtained showed 47, 48, and 50 mg. per 100 c.c. of blood. The renal lesions in these patients were not more severe than in other fatal cases and consisted of thrombosis of arterioles in the medullary portions with infiltration of the large mononuclear cells and polymorphonuclear cells. There was also some tubular epithelial desquamation with resultant plugging of the tubules. As noted above, renal disturbances as reflected in the urine were conspicuously minimal even in those having a fatal termination. The three patients noted above who showed the greatest nonprotein nitrogen retention had only a 1+ albuminuria.

The disease, because of its short duration, was not associated with marked changes in the red blood cells or hemoglobin at the time of admission. However, it is interesting to note that there were no observations of hemoglobins greater than 14 Gm. or polycythemia (red blood cells above five million) in spite of the fact that many of the patients were suffering from lowering of their blood volume as shown by precipitous drops in the red cell counts and hemoglobins which followed within two or three days upon the re-establishment of adequate fluid intake and the administration of parenteral crystalloid and protein solutions. Many of our patients required blood transfusions during the course of their illness because of the fall in the blood counts and the hemoglobin in addition to the value that such therapy had at times in establishing more adequate blood volumes. The anemia which developed was not different from other secondary anemias.

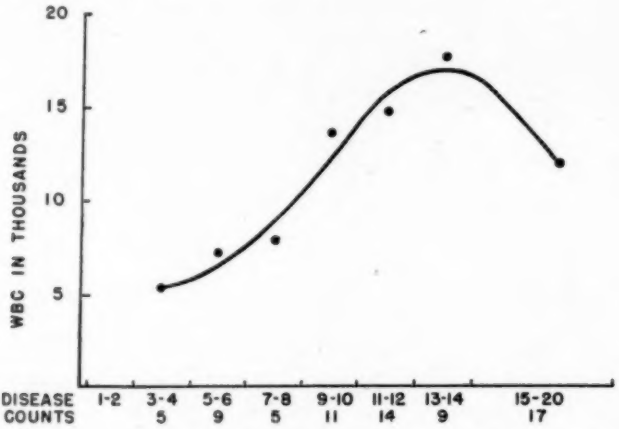


Chart 2.—The white blood cell response in tick typhus according to the day of disease.

The white blood count varied considerably, depending upon the severity of the disease and the stage at which the count was made. Sixty observations were made on our patients and the results are shown in Chart 2.

It is generally stated in textbooks and other clinical descriptions of tick typhus that there is a leucocytosis. Our studies show that during the first week of the disease there is a relative leucopenia. Our counts in the first five days varied from 4,000 to 10,000, with the more severe cases showing the greatest leucopenia. At the end of the first week there is a sharp rise in the white count to average values of 13,700 on the ninth and tenth days, reaching a maximum of 17,800 on the thirteenth and fourteenth days. This leucocytosis falls off sharply after the second week. There was throughout the course a definite polymorphonuclear preponderance, this cell comprising 78 per cent to 90 per cent of the circulating leucocytes, with considerable numbers of stab cells and juvenile cells

being seen even in leucopenic counts. In several instances an increase in the total count on the sixth to seventh day was associated with a fatal outcome but the number of counts involved in our study is too small for this to be accepted as more than a suggestion as to the prognosis. The basic pattern of leucocytic response outlined is similar to that observed by Stuart and Pullem[19] in murine typhus and by Cooke[20] in his report on tick typhus.

Another finding of interest was the change noted in the plasma proteins. A total of twenty-six observations were made at varying stages throughout the course of the disease in nineteen patients. In Table IV is shown the observed values. From these it is apparent that there is a regular lowering of the protein levels and that the albumin-globulin ratio was considerably less than 2:1. These changes are more readily visualized in Chart 3, where the observed values for different periods are averaged and plotted. By the fifth and sixth day, the time of our earliest observations, there was already a lowering of the proteins to nearly the ebb level. After the twelfth day, the observed values were higher but the increase was almost wholly in the globulin fraction, and after the sixteenth day, the observed values for globulin were as high or higher than the al-

TABLE IV. PLASMA PROTEIN IN TICK TYPHUS

CASE NO.	DAY OF DISEASE	TOTAL SERUM PROTEIN	ALBUMIN	GLOBULIN
8	5	5.7	3.7	2.0
9	6	4.1	2.2	1.9
10	6	4.9	2.5	2.4
13	6	6.2	3.8	2.4
13	10	5.8	3.5	2.3
13	16	6.5	3.5	3.0
5	7	4.6	3.0	1.6
5	11	4.9	2.8	2.1
5	13	6.0	3.6	2.4
15	8	4.8	2.7	2.1
17	8	6.2	3.8	2.4
18	8	5.5	3.2	2.3
18	12	5.5	2.9	2.6
11	9	5.0	3.0	2.0
16	9	5.1	3.4	1.7
16	15	5.4	2.9	2.5
19	9	4.7	2.7	2.0
19	13	6.0	3.5	2.5
7	11	5.3	3.1	2.2
12	11	4.7	2.6	2.1
12	18	5.8	2.6	3.2
12	21	7.0	3.4	3.6
12	38	6.9	3.9	3.0
14	11	4.7	2.4	2.3
14	18	5.7	3.2	2.5
22	11	4.1	2.4	1.7
22	14	4.2	2.5	1.7
22	16	4.9	2.9	2.0
22	22	5.6	2.8	2.8
21	12	3.9	2.4	1.5
6	16	5.9	3.3	2.5
20	15	5.9	3.1	2.8
25	15	5.7	3.2	2.5
25	16	5.8	3.2	2.6
25	18	7.2	3.6	3.6

bumin values with a ratio of about 1:1. That individual patients follow a similar pattern is shown in Chart 4, where the cases having multiple observations are shown.

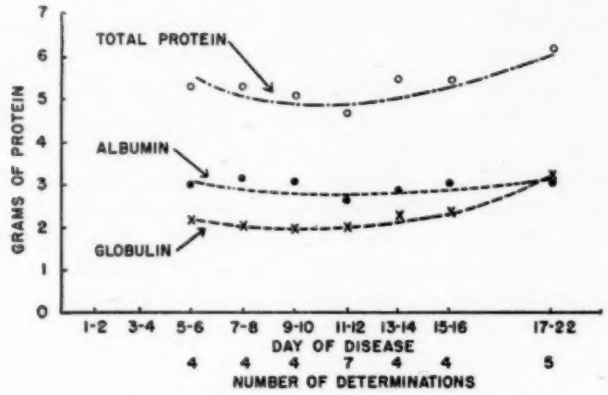

TOTAL PROTEIN
ALBUMIN
GLOBULIN
GRAMS OF PROTEIN
0 1 2 3 4 5 6 7
1-2 3-4 5-6 7-8 9-10 11-12 13-14 15-16 17-22
DAY OF DISEASE
4 4 4 7 4 4 5
NUMBER OF DETERMINATIONS

Chart 3.—Serum proteins during the course of tick typhus.

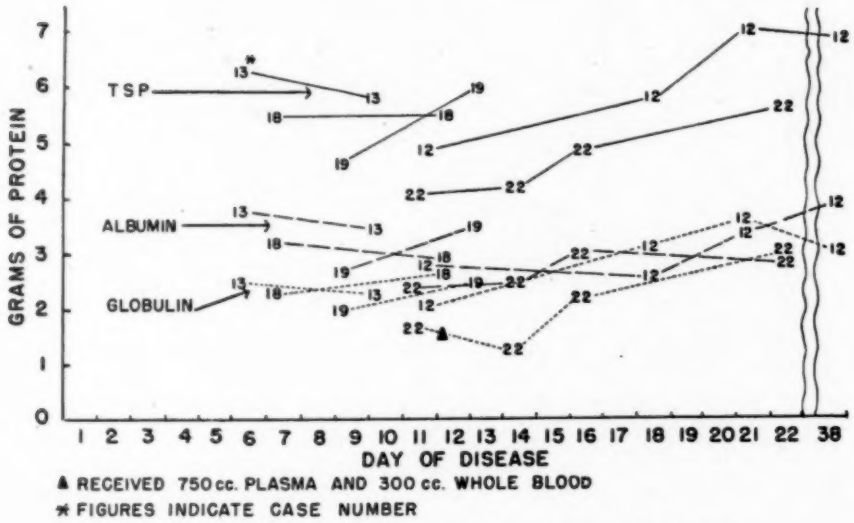

TSP
ALBUMIN
GLOBULIN
GRAMS OF PROTEIN
0 1 2 3 4 5 6 7
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 38
DAY OF DISEASE
▲ RECEIVED 750 cc. PLASMA AND 300 cc. WHOLE BLOOD
* FIGURES INDICATE CASE NUMBER

Chart 4.—Individual serum protein variations in the course of tick typhus.

It seems apparent that these changes in the plasma proteins are related in a considerable degree to the increased permeability of the vascular bed and to the loss of protein into the tissues. That this is not the only factor involved, however has been shown by the studies of Harrell[21] and his associates, who have

shown that this plasma protein depletion can be minimized by a very high protein intake. The liver injury probably also contributes importantly to this difficulty in maintaining the plasma proteins.

The encephalomeningitis noted on physical examination was reflected in the changes observed in the spinal fluid. Thirty-six observations were made on twenty-four of the patients. Two-thirds (twenty-five) of the observations showed moderate degrees of pleocytosis. Of the eleven counts showing normal values of less than 5 cells, six were in patients in whom another observation, later or in one case earlier, showed definite pleocytosis; one was in a patient treated early and successfully with para-aminobenzoic acid; two were on patient Number 1 on consecutive days (this child, two days later at necropsy examination, showed marked meningeal changes); the others were single observations on patients on the fifth and eighth day. The scatter of these observations is shown in Chart 5.

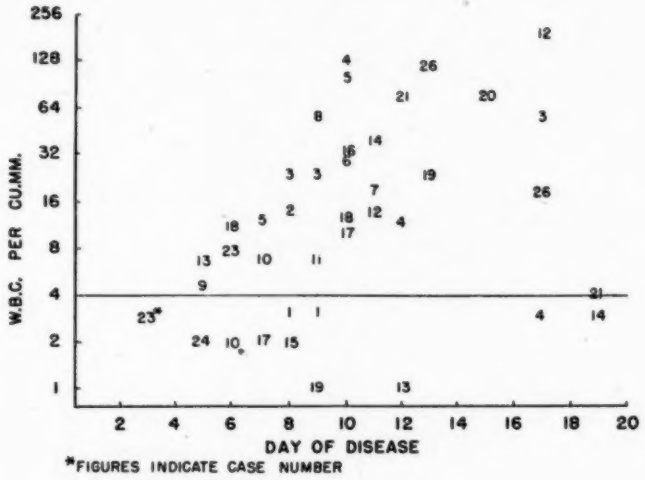


Chart 5.—Spinal fluid pleocytosis in tick typhus.

The character of the cellular response varied considerably; usually most of the cells were lymphocytes, but occasionally in slightly elevated counts early in the course of the disease there was a preponderance of polymorphonuclear cells. The maximum cell count was 182 in a very severe but nonfatal case on the seventeenth day. The cellular response was usually associated with an increase in protein, usually 1+ or 2+ positive Pandy tests. In eight instances where the spinal fluid proteins were observed quantitatively, the response varied from 30 to 189 mg. with an average value of 79 mg. Quantitative sugars were observed more frequently and were usually thought to be normal on simple estimation. The sugar levels varied from 48 to 76 with an average of 58 mg. per 100 c.c.

It is apparent from this study that there is regularly a spinal fluid pleocytosis and increase in the protein. In respect to the cerebral involvement, tick typhus is more like epidemic typhus than is murine typhus.

Our patients were all examined for their antibody response to the infection as measured by proteus OX_{19} agglutinations and some by agglutinations versus proteus OX_2 and OX_k and in later years for the development of complement fixing antibodies against *Rickettsii* and *R. mooseri*.

Two proteus agglutinations done in our own laboratories, the Tennessee State Department of Health Laboratories, and the National Institute of Health Laboratories, have shown considerable variations in the degree of response and as to whether the titer was greatest against one proteus variant or another. This test usually becomes positive by the eighth to tenth day, but occasionally not until the end of the second week. It is probable that the immunologic immaturity of our patients is responsible for this delay as contrasted to the appearance of these agglutinins in adults. The test is useful in establishing the diagnosis of rickettsial infection, but is nonspecific. No combination of proteus agglutinations can serve satisfactorily to establish the identity of a rickettsial infection.

The response with complement fixing antibody occurs later than the proteus agglutination. Again, tests run in different laboratories have shown some variation, chiefly in the titer but also as to specificity. In the earlier tests there was sometimes response to both *R. rickettsii* and to *R. mooseri*. With the improvement in the rickettsial antigens by Plotz and his group,[51] this lack of specificity has disappeared, and at present laboratories usually report little or no crossing of the complement fixation tests. While our material is too small to be worth more detailed analysis, we can with justification say that the complement fixation test is now, in the hands of qualified laboratories,* an adequate and reliable means of establishing the identity of the rickettsial infections. Two samples, one on the fourteenth to seventeenth day of the disease and another on the twenty-first to twenty-fourth day, should invariably yield information to make a satisfactory diagnosis.

Clinical Course.—The cases of tick typhus seem to be devisable into a mild and a severe group and the different groups almost can be separated from the beginning of the infection. Cases 2 to 8 in our group were of the mild group, and we were convinced that the disease was almost always fairly benign in children, but Cases 9 to 16 were of the more severe group and there were four fatalities in the eight cases.

This group of serious cases also came at a time when it was thought that parenteral fluids would overwhelm the circulation, and the patients were not given the benefit of adequate treatment for their circulatory failure. None of the patients with fatal cases lived as long as forty-eight hours after admission to the hospital, and all may be classed as malignant. Two of them died on the sixth day of the disease and two on the tenth day. Of the other fatalities, one

*Tests for complement fixation have been run for us through the courtesy of the laboratories of the Tennessee State Department of Health, the United States Public Health Service Laboratories, and the Virus and Rickettsial Laboratories of the United States Army.

was our first patient, who died on the thirteenth day of her illness with cardiac failure and an overwhelming involvement of the central nervous system; another was our nineteenth patient, who died after ninety-six hours' hospitalization on the thirteenth day of her illness with cardiac failure and widespread pneumonitis; and the seventh was our twenty-fourth patient, who died on the fifth day of her illness, less than twenty-four hours after admission, from a malignant infection. Cardiac failure and pneumonia were obviously present as terminal events. With modern therapy the fatality rate could undoubtedly have been lowered and in some of the patients more vigorous supportive therapy, particularly relating to the prevention of shock and cardiac respiratory failure, might have turned the course of the infection.

In the mild and moderate cases, the patients ran a favorable course from the beginning. The rash was slow to develop purpuric characteristics; the fever as a rule was not more than 104° F.; the patients were stuporous and apathetic but could be easily roused; they took food fairly well and maintained an adequate fluid intake without recourse to parenteral administration; they showed no evidence of myocardial failure and did not tend to develop shock. Most of them began to show improvement in their reactions before the end of the second week of the illness and the fever fell by lysis to normal at an earlier date. The duration of the illness in the mild and in the severe but nonfatal cases, is shown in Table V.

TABLE V. DURATION OF FEVER IN TICK TYPHUS IN SURVIVING PATIENTS

	DAY ON WHICH TEMPERATURE REMAINED LESS THAN 100° F.													
	UNDER 10	10	11	12	13	14	15	16	17	18	19	20	21	OVER 21
Mild cases	1*†	–	–	–	1	–	1	3	–	6	1	–	–	–
Severe cases	–	–	–	–	–	–	1†	–	–	–	1	1	1	2‡

*Eighth day.
†Treated with para-aminobenzoic acid.
‡Twenty-fourth and twenty-sixth days.

The surviving severe cases were distinguished from the mild by their duration as well as by their general course, the fever persisting to the end of the third week and even well into the fourth week. Case 25, whose temperature was normal on the fifteenth day, was the only severe case terminating before the nineteenth day. This early termination was thought to be due to treatment.

Diagnosis.—The diagnosis of tick typhus in the pre-eruptive phase may always be a practical impossibility though a presumptive diagnosis can be made in some cases where one finds an engorged tick attached to the patient or obtains a history of the recent removal, or the handling and particularly the crushing of a tick. Cases of obscure fever occurring in the late spring and early summer in endemic areas should be considered with a high index of suspicion. The sudden onset, the headache, generalized aching pains, and the leucopenic or normal white blood count should serve to call attention to the possibility of tick typhus. The sudden onset should serve to exclude typhoid fevers and variable splenomegaly and freedom from remission should aid in ruling out malaria. In many endemic areas the question of malaria will not enter into the differential diagnosis.

The appearance of the rash will, in almost every case, allow one to make a reasonably certain presumptive diagnosis. The diseases most likely to be confusing are meningococcal sepsis and murine typhus. Meningococcal infections will, as a rule, be differentiated by the associated purulent meningitis, the leucocytosis, and the cultural identification of the organism. Murine typhus on the other hand will be differentiated as a rule by the clinical course, being a much milder disease. The rash in murine typhus is most intense over the trunk, while a peripheral distribution is characteristic in tick typhus. The rash of murine typhus is rarely purpuric, while that of tick typhus is almost always purpuric when fully developed. There will undoubtedly be some cases which can be differentiated only upon the basis of specific laboratory tests.

While it is not the province of this paper to discuss the technique of these laboratory studies, their uses should be enumerated. The rickettsias may be isolated from patients by inoculation of guinea pigs with blood from patients with either rickettsial disease. The animals may become sick with characteristic illness, with or without scrotal lesions.

More practical from the clinician's viewpoint is the differentiation on the basis of serologic study. As mentioned before, the agglutination of proteus OX_{19} serves to establish the infection as a rickettsial disease, and complement fixation studies with specific rickettsial antigens serve to differentiate the rickettsial infection. The uses of these tests were discussed under the section on laboratory findings.

Treatment.—The treatment of patients ill with tick typhus may be divided into two phases, the specific attack on the infection and the general measures needed to combat the profound physiologic disturbances encountered.

Two methods are available for the specific treatment of tick typhus. The first of these was introduced by Topping[22] and is a specific antiserum. To date this serum is available only for experimental observations, but the reports of Topping[22] and Harrell and associates[21] indicate that serotherapy has encouraging possibilities.

The studies of Topping[22] show that serum therapy to be fully effective must be started in the first three days of the rash. He reported the results in the treatment of seventy-one patients, fifty-two of whom received treatment before the third day of the rash and nineteen of whom were treated later. The mortality for the group as a whole was exceptionally low (5.6: the over-all mortality had been shown to be 23.4). Not only was there an improvement in mortality as a whole, but there were fifteen patients in the early treatment group whose fever persisted longer than twenty days, indicating a high proportion of what may be looked upon as severe infections. It should also be pointed out that while both groups were treated, those receiving treatment early showed an average duration of fever of seventeen days, while those receiving delayed treatment had an average duration of twenty days, in spite of the fact that the latter group contained a high proportion of young individuals who are recognized as having a better capacity to respond to the infection. Harrell[21] and his group noted that there was no apparent edema in the individuals who received serum therapy,

thus suggesting that this form of therapy is effective in preventing or at least ameliorating vascular damage. It should be pointed out that the treatment consisted of a single injection of antiserum without any assurance that an adequate or optimal amount was being administered. These studies need extension and repetition. They also emphasize the need for an improvement in diagnosis which will permit earlier treatment.

The second specific therapy for tick typhus is chemotherapy with para-aminobenzoic acid (paba) or sodium paba.* The possibility of using this agent in rickettsial therapeutics was first suggested by Snyder and associates.[23] Hamilton and associates[24] and independently, Grieff and associates[25] showed that paba was effective in preventing the growth of rickettsias in embryo cultures. The studies of Yeomans, Snyder, Murray, Zarafonetis, and Ecke[26] showed that paba was effective in experimental rickettsial diseases and in louse-borne typhus. Anigstein and Bader[27] showed that it was effective in experimental tick typhus. These studies have been followed by several clinical reports showing that paba is effective in treating various rickettsial diseases.

Rose and his associates[28] reported an excellent response to treatment with paba in a severe or moderately severe case of tick typhus. The response was apparent from the precipitious drop in fever on the third day of treatment.

Tierney's study[29] revealed that effective therapy with paba required blood levels of 30 to 60 mg. per 100 c.c., and that such levels could be obtained in adults when 8 Gm. of paba were given as an initial dose followed by 3 Gm. every two hours. In the serious rickettsial disease, scrub typhus, this regime was strikingly effective in the lessening of severe symptoms and complications and in cutting the average duration of the febrile course from twenty to ten days.

In Smith's study[30] of the effect of paba in murine typhus, a smaller dose of drug was used and less dramatic results were obtained. He used 2 Gm. every two hours and did not observe the blood levels obtained. He did obtain shortening of the duration of fever, most notable in patients started on treatment during the first four days of illness.

We have had an opportunity to treat three patients with tick typhus with paba. One of these had a fulminating illness, the patient dying sixteen hours after admission on the fifth day of the disease. One of the others had a mild case, and treatment initiated on the fourth day resulted in prompt response with cessation of fever on the eighth day. The third was a patient who had serious myocardial damage and failure and peripheral vascular failure, but responded more promptly than we could have expected to a combination of supportive measures and paba. He was fever-free on the fifteenth day, four days earlier than any other patient of this category, though treatment was started on the twelfth day of illness. These patients were first seen too late for optimal treatment, but we were impressed by the fact that they seemed much better within twenty-four hours after starting treatment.

We have also observed the effect of paba in three patients with murine typhus not included in this study because they were not children, but mentioned

*Hereafter, paba will be used in place of para-aminobenzoic acid and sodium paba for the sodium salt.

because they exhibited a very satisfactory response to adequate therapy. In these patients the temperature fell to normal in less than seventy-two hours after treatment was started, several days before natural termination could be expected, and one very seriously ill adult showed prompt amelioration of symptoms.

The dosage suggested by Tierney[29] may be translated to children by the graph shown in Chart 6. *From the studies made concerning sulfadiazine therapy, it has been found that the per pound doses for a 10 lb. infant are approximately 3.3 times as high as that for adults,*[31] *assuming that the adults treated by Tierney*[29] *were average in size (150 lbs.). The dosage of 36 Gm. per day were .24 Gm. per pound per day, and infants would be expected, therefore, to need about .8 Gm. per pound per day. It is expected that in older children the dose-weight ratio will follow a curvilinear relationship similar to that illustrated. Our experience as yet does not allow us to offer this curve as a final formulation, but it should serve as a fairly satisfactory means for estimating the maintenance dose needed to bring the infection under control.* In practice, it has been our experience as well as that of Tierney[29] that adequate blood levels are achieved slowly, and it is desirable, therefore, to use a large initial dose.

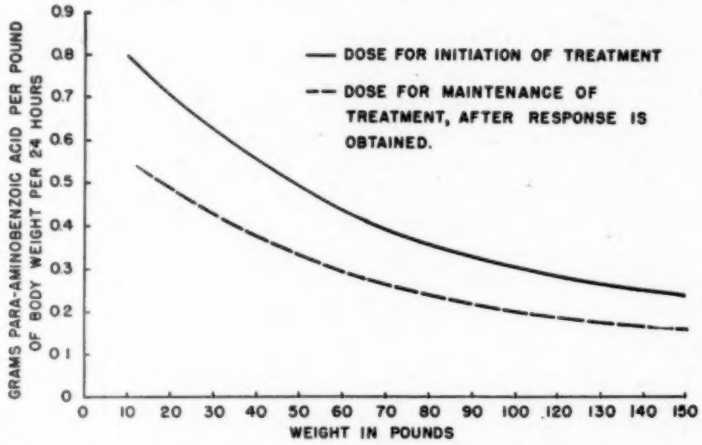


Chart 6.—The dosage of para-aminobenzoic acid in relation to body weight and to the stage of the disease.

The following scheme of therapy, evolved for use in our patients, should yield fairly satisfactory blood levels and prove to be efficacious in the control of rickettsial infections in children.

The total daily dosage, calculated from the initiation level of Chart 6 is divided into twelve doses to be given at two-hour intervals and three times the individual dose is administered as the initial dose. This level of therapy should be maintained until the patient has been fever-free for twenty-four hours. The dosage may then be reduced 25 to 30 per cent or to the level shown for maintenance of treatment after response. The blood levels of the drug should be followed and adjustments should be made to secure levels of 30 to 60 mg. per 100

c.c. during the late phases of active therapy. Therapy should be continued for some time after a remission of fever is secured to prevent relapses, probably for not less than four to eight days, depending upon the general severity of the infection.

While no serious toxic manifestations have been noted from paba therapy, mild confusion was noted by Tierney[29] and lowering of the white blood count has been noted by several investigators.[29, 30] Lowering of the polymorphonuclear leucocytes to 2,500 or less per cubic millimeter should serve as a warning to stop therapy or to lower the intake and proceed with caution. It should also be pointed out that paba is excreted in the urine with base and large doses may lead to the development of profound acidosis. The current trend is to use the drug as the sodium salt, sodium paba, instead of as the free acid, and this should obviate this difficulty. Where the plain paba is used, the alkali intake should be supplemented with sodium bicarbonate at the rate of 2.5 to 10 Gm. or more per day to maintain an alkaline urine. Fluid intake should be increased when levels of over 70 are obtained to accelerate the excretion of the drug.

The general supportive treatment of patients with tick typhus is not less important than the specific measures which may be used.

The increased protein needs of these patients has been stressed by Harrell and his associates.[21] They have shown that protein intakes as high as 9 Gm. per kilogram per day may be inadequate to maintain the serum proteins in these patients, but that such a high protein intake simplified the treatment needed to prevent peripheral circulatory failure. We heartily concur in this need for high protein intakes in these patients. These patients should be given a diet high in protein, low in fat, high in free sugars, and having a high caloric value.

This dietary regime unfortunately can only be applied after considerable protein depletion has occurred, and will not serve to combat the peripheral vascular collapse so often found at the time of admission.

This can be countered only by the adequate use of protein-rich fluids (plasma and blood) which will rebuild the blood volume. The magnitude of protein loss in these patients approaches that seen in severe burns and in extreme diarrheal disease and can be combated best by the free administration of large volumes of plasma. The earlier studies of Topping[22] in experimental animals and in patients have shown that the administration of crystalloids intravenously may be associated with a lessening of the patient's chances for recovery. Whether this is associated with an increase in the vascular loss of proteins or with cardiac failure induced by sudden overloading of the heart one cannot surmise from the report. We suspect the first factor to be most important, but we appreciate the real dangers of cardiac failure in these patients.

It is our belief, based on pathologic observations, electrocardiographic findings, and clinical evidence of cardiac failure, that all patients seriously ill with tick typhus should be digitalized. This should be one of the first therapeutic steps in such patients and may be carried out concurrently with the correction of the depleted blood volume.

The larger volumes of plasma and blood which are needed in this correction should be added to the circulation with great care to avoid overloading the heart.

The generalized vascular lesions of the lungs as well as the presence of myocarditis make it imperative to give intravenous infusions slowly.

All other measures useful in combating peripheral vascular collapse, oxygen therapy, large doses of vitamins, especially thiamine and ascorbic acid, and adequate intake of calories, are also important in treating these patients.

In conjunction with the notes on therapy, it should be pointed out that sulfonamide drugs are contraindicated in these patients. It has been shown in experimental animals by Topping[32] and by Steinhaus and Parker[33] that sulfa drugs were inimical to recovery. Martin[34] reported a patient who responded adversely to sulfa drugs and several of our patients were apparently made worse by the administration of sulfa drugs prior to hospitalization.

Prevention.—The prevention of tick typhus presents a difficult and complex problem but certain simple rules may be outlined which will aid in lessening the dangers of infection. For most of the country the problem will continue to exist, perhaps in increasing intensity, as it is as yet very difficult if not impossible to eradicate ticks.

For those who must live and work in tick-infested environments, especially in localities where prior cases have been known, there is available a vaccine. This vaccine, developed by Spencer and Parker[35] and improved by Cox,[36] is effective in producing a relative immunity and in bringing about an infection of lessened severity where it fails to protect.[37] Regular, frequent, and systematic search for ticks on the body and their removal should be practiced.

People living and working in such circumstances should make every effort to keep ticks off their bodies by wearing clothes which cover the body, tucking them into shoes and in at the waist. Occasional inspection of the neck will then enable them to keep the ticks off. Ticks, when encountered, should not be handled with fingers, especially should not be crushed. Dogs and other animals should be deticked by insecticides instead of the common practice of picking them off.

MURINE TYPHUS FEVER

General Considerations.—Murine typhus in man is an acute, self-limited, infectious disease. The etiologic agent is the obligate intracellular parasite, *R. mooseri.* This rickettsia characteristically infects rodents, particularly rats and their ectoparasites.[38] It is transmitted from rat to rat by ectoparasites, principally *Xenopsylla cheopis,*[38] and the rat louse, *Polyplax spinulosis.*[39] The disease is transmitted from the rat to man by the accidental parasitization of man by one of the ectoparasites of the rodent.

The reports of Brill in 1889[40] and 1910[41] first called attention to the fact that there was a mild, noninfectious, typhuslike disease in New York. Subsequent studies by Paullin,[42] Newell and Allen,[43] McNeill,[44] and others,[45, 36] showed that this disease was also present in the South. It was, however, the studies of Maxey[47] in 1926 that really focused attention upon and brought out the real problem presented by this infection. There has been, since that time, as was pointed out by Meleney,[48] a rapid extension of the disease to involve new areas and to become more prevalent in the areas where it is endemic.

Maxey's study[47] on purely epidemiologic grounds pointed to rodent population of urban centers as the reservoir for the infection and to some ectoparasite of rodents as the vector. The studies of Dyer and associates[49] incriminated the rat and the rat flea, *X. cheopis*. Subsequent studies have further substantiated this combination as being principally responsible for the spread of this mild form of typhus fever, now generally called murine typhus. The studies of Dove and Shelmire[50] indicate that the rat mite, *Liponyssus bacoti*, which attacks man, is also capable of passing the infection.

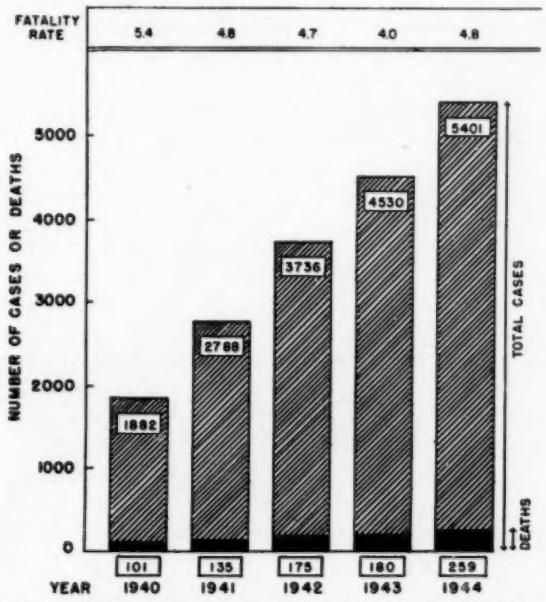


Chart 7.—Cases of and deaths from murine typhus fever in the United States from 1940 through 1944.

The relationship of murine typhus to epidemic typhus is not as yet entirely clear. The development of modern technique for serologic identification of these infections by complement fixation and specific rickettsial agglutination[51] has led to the conception that they are due to closely related organisms but that the organisms are not derivatives of one another. The previously held belief that murine typhus is the result of rodent adaptation of the rickettsiae of epidemic typhus is probably not valid, at least louse transmission of murine typhus does not bring about a reversion to the more severe epidemic typhus.[54]

The problem of typhus fever in this country is wholly that of murine typhus. The problem of murine typhus on the other hand is world-wide and in most parts of the world is complicated by the concomitant presence of epidemic typhus fever. Murine typhus is a danger or potential danger wherever rats are found.

Chart 7 shows the cases of murine typhus reported in the United States in the years 1940 through 1944. The geographic distribution of this infection in the United States is shown in Fig. 6. From this it is apparent that typhus is now chiefly important in the southern states and in the seacoast states except that states north of New York in the east and the sections north of Los Angeles on the west have not yet become areas of serious endemic infection.

In the South the disease has spread from urban centers to the rural sections. It is probable that the disease will increase greatly unless concerted efforts are made to eradicate the rat population. The apathy which is manifested in many areas concerning this problem would make it seem unlikely that relief will occur from this source until the problem becomes worse.

Fig. 6.—Geographic distribution of murine typhus fever in the United States (1940 through 1944).

While there are not adequate studies to show the frequency of typhus fever in children, the study of Baker and associates[52] in Alabama and of Meleney and French[53] in California, indicate that about 10 per cent of the cases are in children. The disease is, as has been shown by Scoville,[54] Esky,[55] and Davis and Pollard,[56] greatly underreported and underrecognized; and as children have milder infections than adults, it is probable that morbidity in children is considerably in excess of reports. Our own experience bears this out, as we surely missed cases before Scoville's[54] work called to our attention the presence of the disease in infants we were following for mild fever of unknown origin.

There is a distinctive seasonal pattern to the distribution of cases. In earlier studies, Baker and associates[52] were able to show ten times as many cases in September as in February. In recent years there has been less difference, though the greatest incidence is still in the summer and fall months. This is related in part to the degree of parasitism of rats with *X. cheopis*.[57] The seasonal distribu-

TABLE VI. SEASONAL DISTRIBUTION OF REPORTED CASES OF MURINE TYPHUS FEVER IN THE UNITED STATES, 1940 THROUGH 1944

JAN.	FEB.	MAR.	APRIL	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.
679	1,039	615	565	836	1,125	2,109	2,822	2,634	2,286	1,930	1,729

tion of reported cases for 1940 through 1944 is shown in Table VI, composed of figures taken from Public Health Report supplements. From this table it is apparent that cases are prevalent throughout the year but that there are five times as many cases in August, the peak month, as in April, the ebb month.

Pathology.—The pathologic disturbances found in murine typhus should provide a background for the understanding of the clinical manifestations. But as at the time of Brill,[41] the pathology of the disease is unknown. Textbooks conveniently refer, without documentation, to a carried-over statement that it is similar to but milder than epidemic typhus. We have been unable to find any protocols of the pathologic histology of murine typhus infections in man. In this city, two cases of typhus have been examined post mortem, both were adults in whom the chief cause of death was cardiac failure and in whom the vascular lesions were minimal. As neither was a completely identified case of typhus, they are not available for detailed study of the pathologic manifestations of the disease. Stuart and Pullen[19] indicate that biopsies of the skin in murine typhus show rickettsias in the vascular endothelium but not in the smooth muscle cells, but they do not cite references.

Clinical Considerations.—The onset in murine typhus is abrupt as a rule, with headache, a sense of illness or malaise, abdominal discomfort with nausea and vomiting, chilly sensations, and sore throat being the subjective symptoms noted at the onset. The headache is the most distressing symptom and persists throughout the major part of the illness and was present in most cases. Fever is usually noted immediately after the malaise and headache appear.

Only three of our patients were seen by a physician before admission, one by us as an outpatient and two by other physicians. In each instance the child was treated for a respiratory infection, for sore throat or bronchopneumonia, with sulfonamides.

The children were as a rule apathetic rather than being seriously ill and did not complain much if left alone, which probably accounts for the fact that they were not seen earlier for medical care. Perhaps this may also serve as an index of the degree of severity of the infection.

The fever in our cases varied between 101° and 105° F., and was usually between 102° and 104° F., with a daily variation of 1 to 3° F. The fever tended to swing more widely in the two days before the rapid lysis of one to two days which terminated the fever. Fever persisted for nine days in two instances, eleven days in four, twelve and thirteen days in one each, fourteen days in two, fifteen days in one, and nineteen days in one.

The rash, which is the single specific manifestation of the disease from a clinical viewpoint, appeared from the third to seventh day. In two instances the family had not noted the rash and in one instance the rash was the first symptom noted. The rash is usually thought to appear first on the trunk, usually the

abdomen, and spread peripherally, but our patients did not conform. The rash appeared first on the face or extremities in four instances, first on the trunk in five instances, and was generally distributed when first observed in three instances. The skin lesions were usually pink to red macules 2 to 5 mm. in diameter. These blanch incompletely on pressure but showed purpuric tendencies in only two instances. The rash was usually composed of scattered lesions and was most intense on the abdomen. The rash usually faded, leaving slight brown staining of the skin at the time the temperature began to swing or about seventy-two hours before the fever disappeared.

While these patients were usually quite apathetic throughout the febrile period, coma was not noted at any time, and only two patients could be called stuporous.

Two were brought in with a complaint of stiffness of the neck and slight stiffness was noted on two others at admission. The spinal fluid was examined in seven cases, with a total of eight examinations, on the sixth to eleventh day of the disease, and showed 3, 3, 4, 4, 4, 5, 6, and 8 lymphocytes with 19 to 25 mg. of protein and 55 to 64 mg. of sugar. All evidence of meningeal irritation disappeared with the cessation of fever.

TABLE VII. SERUM PROTEIN DETERMINATIONS IN MURINE TYPHUS

PATIENT	TOTAL SERUM PROTEIN	ALBUMIN	GLOBULIN	DAY OF ILLNESS	COMMENT
T 1	7.1	3.9	3.2	7th	Markedly dehydrated
T 2	6.0	3.3	2.7	7th	Edema of face
T 3	6.0	4.2	1.8	5th	
T 5	6.3	4.1	2.2	5th	
T 6	5.7	3.4	2.3	10th	
T 9	5.9	3.5	2.4	5th	

In two patients, edema of the face was noted. In both instances this was only slight. Serum proteins were determined in six patients (see Table VII). It is apparent from these few observations that while there may be slight to moderate hypoproteinemia in murine typhus, the changes are much less constant and are less marked than in tick typhus. There was not in any of the murine typhus group a shocklike state, though several were mildly dehydrated from poor fluid intake and vomiting. Patient 1 was markedly dehydrated. It is interesting that even in this group with relatively mild arterial lesions the proteins tended to be low and there was a shift of the albumin-globulin ratio toward unit. This suggests that here, as in tick typhus, the principal vascular lesion is one of capillary injury.

There was no evidence of significant renal injury. Patients 1 and 3 showed a slight transient albuminuria. No renal function tests were performed, but in four instances the nonprotein nitrogen was determined, ranging from 27 to 31 mg. per cent.

While five of the twelve complained of sore throat, the examination of the respiratory tract was negative except that ten of the twelve were noted to have some pharyngeal congestion. Chest roentgenograms made in four instances showed only very slight increase in the bronchovascular markings.

There was no evidence in any of our murine typhus cases of cardiac embarrassment. Tachycardia was a usual accompaniment of the fever, but there was no engorgement or tenderness of the liver. Electrocardiograms were made in six instances and showed only slight decrease in the voltage and once minor aberrations in the S-T segment. None showed significant prolongation of the P-R interval.

A number of laboratory studies were carried out on these patients, some of which have already been mentioned and need no further review. The serologic studies which are diagnostic and the hematologic studies warrant review.

There was no particular change in the red blood cells or hemoglobin which could be attributed to the disease. The white blood cells tended, as has been pointed out by Stuart and Pullem,[19] to be low in the first week and then to rise at the end of the second week. Admission counts on the fifth to seventh day were 4,850 to 13,800, with an average of 7,100. Eight of the twelve counts were less than 6,500. Five counts made from the eighth to the tenth day were 5,350 to 9,150, with an average of 6,050, and four counts made on the eleventh to the thirteenth day were 6,500, ± 1,200.

All patients were examined for their serologic response to the infection as measured by Proteus OX_{19} agglutination and with two exceptions by complement fixation with the *R. mooseri* antigen. Some were also checked for complement fixation against *R. rickettsii* antigen and the reactions were found to be reasonably specific in this respect. Occasionally much lower titers of heterogenous rickettsial complement fixation were observed. The complement fixation tests were performed by several laboratories employing antigens of variable sensitivity and specificity. Our series of tests, while not large, indicate that agglutination of Proteus OX_{19} usually occurs by the tenth day in ten out of twelve patients. A single positive complement fixation test was obtained as early as the tenth day.

In the performance of serologic tests one should remember that the Proteus OX agglutinations, while responding more quickly than complement fixation tests, are of no etiologic significance other than to establish the fact that the patient has a rickettsial disease.

The relative sensitiveness of these tests is shown in the following serologic response charts* (Charts 8 and 9). It is apparent from these charts that there are some cross-reactions between the complement fixation of antigen from *R. mooseri* and from *Rickettsia prowazeki*, and that single determination of low titers might not be specifically significant.

Epidemiologic Notes.—Most epidemiologic studies of murine typhus state that multiple household cases are rare, but in our series there were four examples of multiple household infections. Two of our patients were sisters admitted at an interval of more than a year. In one instance there had been three previous cases in the same house. One child was admitted at the same

*These studies were carried out by the Division of Virus and Rickettsial Disease of the Army, and were made available to us through the courtesy of Major A. D. Scoville.

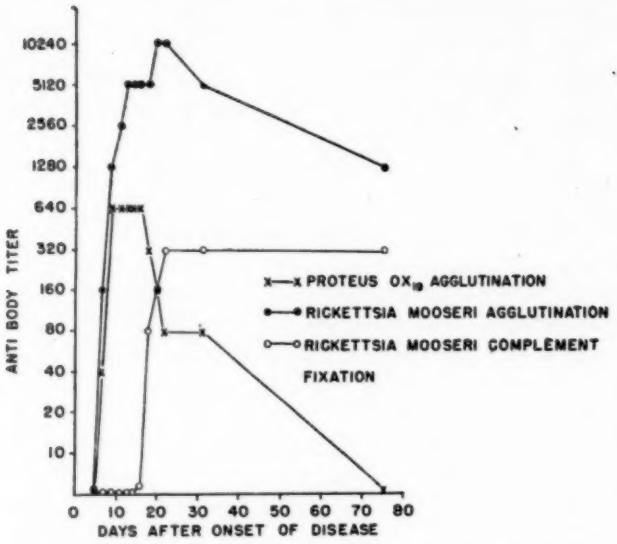


Chart 8.—Antibody response during the course of murine typhus: a comparison of various serologic tests. Case 7.

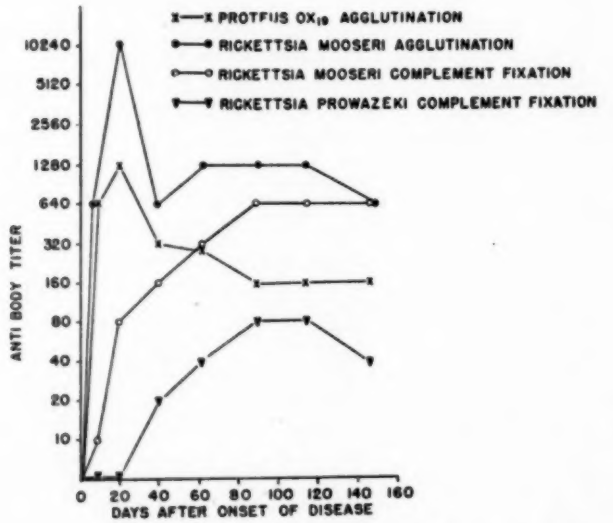


Chart 9.—Antibody response during the course of murine typhus: a comparison of various serologic tests. Case 8.

time as her mother, also ill with typhus, and a brother had had typhus several months earlier. In the other instance, an older sister in the family was recovering from the infection when our patient was admitted. There was no evidence of lousiness in any of our patients. Also, most studies indicate that males are affected more often than females, probably due to the fact that most of the infections considered were the result of infection derived from work association with infected rats. In Nashville, cases originate not only from work association but in some sections from infected rats in residential areas. Scoville[54] has noted that in typhus occurring in such areas the usual preponderance of male cases is reversed and that more women were infected than men. In our group, eleven of the twelve cases were girls. This suggests that the clothing worn by girls makes them more readily attacked by the rat flea, or that their activities in the home are more likely to bring them into contact with the rat fleas. The numbers involved are small but this preponderance is quite startling and significant.

Differential Diagnosis.—The diagnosis of murine typhus ultimately rests upon laboratory tests. From the clinical viewpoint, it is essential that a high index of suspicion be maintained; to be recognized it must be kept in mind in all unexplained febrile illness, and even so it will usually be impossible to more than postulate the possibility until the rash appears. The most difficult differentiation with tick typhus was considered in the preceding section.

The disease otherwise is most apt to be confused with exanthum subitum, measles, and drug rashes. In the first of these, marked hyperirritability rather than apathy is the rule, in measles the presence of enanthem and severe coryzeal symptoms should be enough to differentiate the infections. The present custom of treating all patients with infectious processes with sulfonamides makes it most difficult to rule out drug rashes; even the cases of typhus are apt to have been subjected to this treatment. The rash from sulfadiazine would be most likely to be confusing, and that of sulfathiazole rarely if ever. In the most severe cases with hemorrhage into the lesion one might suspect meningococcemia, but here the attendant, relative leucopenia of typhus should be helpful in the differentiation. Typhoid fever with abundant rose spots may at times be confusing but fortunately in this phase the blood culture will almost invariably be positive.

The correct diagnosis could be made eventually by the clinical course of the disease in most instances, but in some sections of the country the severe cases of murine typhus will be confused with mild cases of tick typhus. This differentiation can be made only by the isolation and identification of the specific rickettsia or by running simultaneous serologic tests for antibodies for both rickettsias on the serum, preferably eighteen to twenty-four days after the onset. The fact that the disease is due to rickettsia can probably best be established by the use of Proteus OX_{19} agglutinations, a simple test which can be run by any reliable bacteriologic laboratory. The differential diagnosis on the basis of agglutination of strains of Proteus other than OX_{19} has fallen, justifiably, into disrepute.

Treatment of Typhus.—The fatality rate for murine typhus fever is very low, none in 180 cases reported by Stuart and Pullem.[19] Recovery, in practically

all childhood cases, will ensue with simple expectant treatment which maintains an adequate fluid balance and a reasonable food intake, particularly a high protein intake. This feeding should be by gavage if necessary. Early in the disease the problem of vomiting and associated ketosis may require parenteral administration of glucose, plasma, and saline to reestablish satisfactory metabolic activities and to restore the interstitial fluids. This will be necessary, however, only rarely.

The general outline of therapy for patients with tick typhus is applicable to the more severe cases.

However, even with satisfactory supportive therapy, the disease is a protracted illness with two weeks or more of fever followed by a convalescence period proportional to the age of the patient, which makes the advent of specific therapy highly desirable. The experiences with immune sera in the treatment of epidemic typhus and spotted fever have shown that to be effective these must be given in the first four days of the illness. The practical difficulty in making a diagnosis in this period will almost certainly preclude usefulness of this agent in murine typhus; to say nothing of the costs of such therapy. The observations of Hamilton and associates[24] that paba is effective in inhibiting the lethal effect of *R. mooseri* in the development of chick embryo, and study of Smith[30] showing that murine typhus fever responds to paba when it is administered in the first week of the illness, encourage us to think that the drug will be effective treatment. To be effective, however, early diagnosis and treatment are essential. Our experience with paba therapy in murine typhus in childhood is limited to one patient. This child was treated adequately from the beginning of the fourth day and was fever-free on the sixth day. The technique of using the drug was discussed under the section on tick typhus and needs no repetition here.

Prevention.—While laboratory studies indicate that a vaccine would be effective in preventing murine typhus, a more rational approach to the problem would be the systematic eradication of rats.

CONCLUSIONS

A review of the rickettsial diseases of childhood reveals that the problem of tick typhus is now common to the whole of the United States and to some areas of Central and South America. The extent of the problem of murine typhus is not now clear, but it probably extends to most of the warmer temperate zones.

Tick typhus is a serious disease with a high mortality even in childhood. A thorough knowledge of the principal pathologic lesions and their relationship to the clinical manifestations of the disease should lead to a more satisfactory handling of these patients. Early recognition of the disease will allow the effective use of paba either alone or in conjunction with serum therapy for the treatment of these patients. To make this early diagnosis the clinician must exercise a high degree of suspicion. It is probable that the increase in travel and utilization of our outdoor recreational facilities, again available to the public, will increase the number of cases of tick typhus.

Murine typhus in the far South is so greatly under-recognized or unreported that we have very little concept of its relation to the practice of medicine. Very likely the disease is masquerading under a wide variety of aliases or exists in a form not now recognized. Though no more than 10 per cent of the cases occur in childhood, one may safely estimate that 5,000 cases occur yearly in children in the United States, chiefly in the southern states. Even though it is a mild disease, its recognition and correct treatment would serve to bring about better medical practice and to emphasize the need for the extermination of rats.

SUMMARY

1. The clinical manifestations of tick typhus and murine typhus in childhood have been presented and have been correlated, in so far as is possible, with the pathologic and clinical pathologic manifestations of the disease.

2. The general treatment of rickettsial infections in childhood has been presented, together with an outline for the use of para-aminobenzoic acid in these infections.

REFERENCES

1. Wood, W. W.: Report of the Surgeon-General of the Army to the Secretary of War, 1896.
2. Maxey, E. E.: Med. Sent. 7, No. 10, 1899.
3. McCullough, G. T.: Med. Sent. **10**: No. 7, 1902.
4. Wilson, Louis B., and Chowning, Wm. M.: J. A. M. A. **39**: 131, 1902.
5. Anderson, John F.: U. S. P. H. S. and Marine Hosp. Service, Hyg. Lab. Bull. No. 14, 1903.
6. Stiles, C. W.: U. S. P. H. S. and Marine Hosp. Service Hyg. Lab. Bull. No. 20, 1905.
7. Contributions to Medical Science by Howard Taylor Ricketts 1870-1901; published as a tribute to his memory by his colleagues under the auspices of the Chicago Pathological Society, 1911, University of Chicago Press.
8. Wolbach, S. B.: J. Med. Research **41**: 1, 1919.
9. Badger, L. F., Dyer, R. E., and Rumreich, A.: Pub. H. Rep. **46**: 413, 1931.
10. Rumreich, A., Dyer, R. E., and Badger, L. F.: Pub. Health Rep. **46**: 470, 1931.
11. Litterer, in an unpublished investigation of the first cases of Rocky Mountain spotted fever in Tennessee, reported from Giles County in 1931, found that a pack of hounds had been brought to that area from the Bitter Root Valley of Montana the preceding year.
12. Jellison, W. L.: Pub. Health Rep. **60**: 958, 1945.
13. Topping, Norman H.: Pub. Health Rep. **56**: 1699, 1941.
14. LeCount, E. R.: J. Infect. Dis. **8**: 421, 1911.
15. Harris, P. N.: Am. J. Path. **9**: 91, 1933.
16. Lillie, R. D.: Nat'l Institute of Health Bull. No. 177, 1941.
17. Allan, A. C., and Spitz, Sophie: Am. J. Path. **21**: 603, 1945.
18. McCalla, F. P.: Med. Sent. **10**: 1908.
19. Stuart, B. M., and Pullem, R. L.: Ann. Int. Med. **23**: 521, 1945.
20. Cooke, Jean V.: Yale J. Biol. & Med. **16**: 495, 1944.
21. Harrell, T., Wolff, Wm. A., Venning, W., and Rimhart, John B.: South. Med. J. **39**: 551, 1946.
Harrell, G. T., Venning, Wm., and Wolff, Wm. A.: J. A. M. A. **126**: 929, 1944.
22. Topping, Norman H.: Pub. Health Rep. **58**: 757, 1943.
23. Snyder, J. C., Maier, J, and Anderson, C. R.: Report to the Div. of Med. Sc., Nat'l Research Council, Dec. 26, 1942.
24. Hamilton, H. L., Plotz, H., and Smadel, J. E.: Proc. Soc. Exper. Biol. & Med. **58**: 255, 1945.
25. Grieff, D., Pinkerton, H., and Moragues, V.: J. Exp. Med. **80**: 561, 1944.
26. Yeomans, A., Snyder, J. C., Murray, E. S., Zarafonetis, C. J. D., and Ecke, R. S.: J. A. M. A. **126**: 349, 1944.
Snyder, J. C., and Zarafonetis, C. J. D.: Proc. Soc. Exper. Biol. & Med. **60**: 115, 1945.
Murray, E. S., Zarafonetis, C. J. D., and Snyder, J. C.: Proc. Soc. Exper. Biol. & Med. **60**: 80, 1945.
27. Anigstein, L., and Bader, M. N.: Science **101**: 591, 1945.

28. Rose, H. M., Duane, R. B., and Fischel, E. E.: J. A. M. A. 129: 1160, 1945.
29. Tierney, N. A.: J. A. M. A. 131: 280, 1946.
30. Smith, Paul K.: J. A. M. A. 131: 1114, 1946.
31. Peterson, J. C.: Unpublished observations.
32. Topping, N. H.: Pub. Health Rep. 54: 1143, 1939.
33. Steinhaus, E. A., and Parker, R. R.: Pub. Health Rep. 58: 351, 1943.
34. Martin, D. W.: J. PEDIAT. 16: 468, 1940.
35. Spencer, R. R., and Parker, R. R.: Studies on Rocky Mountain Spotted Fever. Hygienic Lab. Bull 154, 1930, Government Printing Office.
36. Cox, H. R.: Pub. Health Rep. 54: 1070, 1939.
37. Parker, R. R.: J. Infect. Dis. 57: 78, 1935.
38. Dyer, R. E., Rumreich, A., and Badger, L. F.: Pub. Health Rep. 46: 334, 1931.
39. Mooser, H., Castenada, M. R., Zinseir, H.: J. Exper. Med. 55: 567, 1931.
40. Brill, N. E.: N. Y. Med. J. 67: 77, 1898.
41. Brill, N. E.: Am. J. M. Sc. 139: 484, 1910.
42. Paullin, J. R.: South. Med. J. 6: 36, 1913.
43. Newell, L. B., and Allen, W.: South. Med. J. 7: 564, 1914.
44. McNeill, H. L.: Texas State J. Med. 12: 188, 1916.
45. Allen, W.: South. Med. and Surg. 85: 65, 1923.
46. Maxey, K. F., and Havens, L. C.: Am. J. Trop. Med. 3: 495, 1923.
47. Maxey, K. F.: Pub. Health Rep. 41: 1213, 1926.
Pub. Health Rep. 41: 2967, 1926.
48. Meleney, H. E.: Am. J. Pub. Health 31: 219, 1941.
49. Dyer, R. E., Ceder, E. T., Lillie, R. D., Rumreich, A., and Badger, L. F.: Pub. Health Rep. 46: 2415, 1931.
50. Dove, W. E., and Shelmire, B.: J. A. M. A. 98: 1507, 1931.
51. Plotz, H., Wertman, K., and Bennett, B.; and Plotz and Snyder in reports to the Director U. S. A. Typhus Commission, Feb. 15, 1944, and Oct. 31, 1944. Cited by Plotz, H., and Wertman, K.: Proc. Soc. Exper. Biol. & Med. 59: 248, 1945.
Castaneda, R. M.: J. Immunol. 31: 285, 1936.
Bengtoon, Ida: Pub. Health Rep. 56: 649, 1941.
52. Baker, J. N., McAlpine, J., and Gill, D.: Am. J. Pub. Health 24: 1068, 1934.
53. Meleney, H. E., and French, R. S.: California & West. Med. 62: 116, 1945.
54. Scoville, A. D.: Personal communications concerning unpublished data accumulated for the Typhus Commission.
55. Esky, C. R.: Pub. Health Rep. 58: 631, 1943.
56. Davis, David E., and Pollard, Morris: Pub. Health Rep. 61: 928, 1946.
57. Rumreich, A. S., and Wynn, R. S.: Pub. Health Rep. 60: 885, 1945.

EARLY EVIDENCE OF PSYCHOSES IN CHILDREN

With Special Reference to Schizophrenia

Charles Bradley, M.D.
East Providence, R. I.

THE pediatrician is likely to be the first consultant, if not the first physician, to see children with incipient serious illness, mental as well as physical. Since psychoses are known to occur in childhood, and are by definition serious mental disturbances, it seems important for the pediatrician to be familiar with their early manifestations. Some of these early manifestations are the subject of the present report, which is based on studies undertaken to determine what types of childhood behavior signify that a psychosis is present or impending.

In spite of all that has been written and said about psychoses, there is no generally accepted definition of the term. Inevitably in such a situation, concepts as to what constitute psychoses vary among different schools of psychological thought. This is very confusing to the nonpsychiatric worker seeking to orient himself and leaves the pediatrician little choice but to select from some reliable source a definition which will be of practical value to him. For the purpose of the studies herein reported, a psychosis is considered "a severe mental disturbance in which all the usual forms of adaptation to life are involved"[1] and in which "disorganization of the personality is extreme."[2]

A great deal more is known about the psychoses of adults than those of children. They are usually classified as organic, toxic, or functional, depending upon the presence or absence of known causative factors. Individual psychoses in each of the three groups have been fairly well delineated and are often discussed as though they were disease entities. Among the cardinal signs and symptoms helpful in the diagnosis of adult psychosis are the patient's lack of insight that he is ill, the presence of delusions and hallucinations, and apparent disturbance of capacity to sense or express emotions (affect). The implication of chronicity and discouraging prognosis that may accompany the establishment of a diagnosis of psychosis is undoubtedly a by-product of the well-known fact that a large proportion of hospital beds the world over are occupied for years on end by chronically psychotic adult patients.

For children we lack a generally accepted classification not only of psychoses but of psychiatric disorders in general. The criteria mentioned above for adult psychoses do not adequately apply to children for whom we must seek other standards of deviation from mental health. Psychiatric diagnostic standards in childhood must be even more flexible than those used with adults. The reactions of mentally ill children can be properly evaluated only in terms of what is anticipated for most children of similar age and maturity, and no single standard scale of normality covers the entire childhood period.

This study was assisted by a grant from the Committee for Research in Dementia Praecox founded by the Supreme Council, 33rd degree Northern Masonic Jurisdiction.

Presented before the Fifteenth Annual Meeting of the American Academy of Pediatrics, Pittsburgh, Pa., Feb. 24-27, 1947.

Children may react to physical illness or injury with behavior which is sufficiently disturbed to warrant the description "psychotic." The delirium which may accompany fever or some of the disturbances which follow head injury are examples. Such disturbances are, however, not usually listed as psychoses. This may be due to their obviously secondary association with more clearly understood physical illness or to their temporary duration. A classification of such reactions as "symptomatic psychoses" has been recently suggested.[1] While it is generally recognized that a child's usual personality doubtless bears some relation to the temporary mental symptoms that accompany physical illness, we lack precise data proving this relationship. On the basis of information now available, no valid prediction of specific mental symptoms which will accompany the physical illness of a particular child is warranted, nor are we able to discuss this subject at a practical level.

On the other hand, there is considerable information available as to some of the early evidences of functional psychosis in childhood. In contrast to the several clearly recognized functional psychoses of adults, schizophrenia is the only one generally accepted as occurring in children before 13 years of age. This psychosis accordingly forms the main subject of the present discussion.

Schizophrenia was a term introduced by Bleuler in 1911 to describe a mental illness apparently based on a disturbed balance or "splitting" of two important groups of the patient's mental characteristics, those by which he deals with the real world around him and those which are devoted to the imaginary world existing only within his own mind. In mentally healthy individuals these two sets of characteristics are maintained in balance supplementing one another toward efficient mastery of actual life situations. The schizophrenic patient becomes preoccupied with his world of fantasy to a degree incapacitating efficient mastery of these real world situations. Kraepelin in 1896 had used the term dementia praecox to describe the illness of many similar patients, emphasizing primarily that it was a mental illness of early life which usually went on to complete incapacity. At present schizophrenia and dementia praecox are for practical purposes employed interchangeably in clinical and literary discussions, in spite of their different derivations. "Schizoid" is a related term used to describe personalities and clinical conditions which may precede, lead up to, or are similar to the psychosis schizophrenia.

As applied to children, schizophrenia is best used to denote a psychosis, that is, a severe mental illness. It has been defined for this purpose as "a rare but severe distortion of the personality peculiarly distinguished by a diffuse retraction of interest from the environment. This may be described in terms of the child's diminution of appropriate affective contact with reality, loss of interest in his surroundings, failure to derive emotional satisfaction from the ordinary events of life, or preoccupation with subjective matters to the exclusion of external situations."[3]

PLAN OF STUDY

The purpose of the present discussion is to furnish the pediatrician with descriptions, reactions, and behavior which indicate that schizophrenia must be

seriously considered in certain children who come to him for examination, with emphasis on the earliest signs of this psychosis.

In searching for important objective evidence of the presence of psychoses in children, the following three plans of study have been pursued: (1) behavior symptoms capable of description in children presumably psychotic at the time of observation have been investigated and evaluated; (2) past histories of children known to be psychotic have been searched for reports of their earliest maladjustment; and (3) a search has been made for reliable notes written on the spot in diaries or baby books describing step by step the growth and reactions of children who later became psychotic, so that the evolution of a psychosis, in terms used by parents to describe what they have seen, might become available.

Portions of the material herein presented have been previously published but are included as integral parts of the present, more complete report.

BEHAVIOR CHARACTERISTICS OF SCHIZOPHRENIC CHILDREN

The initial portion of this study was carried out some years ago and its results published upon completion.[4] Its conclusions have, with minor modifications, since been found valid in a larger number of schizophrenic children over a much wider age range. The project was undertaken to determine just what types of behavior capable of objective description by any intelligent nonbiased observer are characteristic of children whom experienced clinicians have considered to be schizophrenic or schizoid. The investigation concerned 138 maladjusted boys and girls who had been admitted over a period of years for psychiatric study to the Emma Pendleton Bradley Home, a children's psychiatric hospital. All were under 13 years of age and, as resident patients for a period of several months, were free from the immediate effects of family and community pressures and prejudices. Fourteen of these children had been considered potentially schizophrenic by competent clinicians, but their exact criteria for making this diagnosis were variable and often based on intuitive impressions. The study itself was carried out by first tabulating all of the major behavior characteristics of each of these fourteen children as noted in the hospital record. Only reactions capable of description by "persons entirely unfamiliar with each patient's background" were considered. The presence or absence of each tabulated symptom in the total group of 138 children was then checked by several members of the hospital staff who had personally worked with the entire group. The behavior traits whose presence seemed to distinguish the schizophrenic children from the rest were then investigated more carefully.

Eight major behavior characteristics were found to be especially prominent in the fourteen children diagnosed as schizophrenic. These in the order of frequency and apparent importance were as follows:

1. Seclusiveness
2. Irritability when seclusiveness was disturbed
3. Daydreaming
4. Bizarre behavior

5. Diminution of personal interests
6. Regressive nature of personal interests
7. Sensitivity to comment and criticism
8. Physical inactivity

Detailed definitions of these terms appear in the original communication and may be abstracted here:

Seclusiveness is considered as a strong tendency to consistently remain aloof from the society of other children for no obvious constructive reason such as physical incapacity, or pursuit of special projects.

Irritability is considered to be a reaction of anger when the seclusive activities are interrupted, especially by the personal intervention of other individuals.

Daydreaming may be termed apparent preoccupation with thoughts and fantasies definitely beyond what is usually noted in children of similar age and development.

Bizarre behavior is made up of actions and activities decidedly incongruous to the surroundings in which they occur. It includes such phenomena as posturizing, repetitive purposeless motions, unintelligible language, and irrelevant expression of emotion.

Diminution of interests indicates that there are conspicuously fewer objects and activities toward which the child is attracted than one usually anticipates for most children of similar age and intelligence.

Regressive personal interests involve the voluntary selection of and participation in amusements and occupations customarily intriguing children of younger age levels.

Sensitivity to comment and criticism implies an excessive emotional response to the personally directed opinions of others such as praise, blame, and so on.

Physical inactivity indicates conspicuously less gross motility than is commonly seen in other children of similar age and development.

To illustrate the manner in which these characteristics were noted to be present in one of the children of the schizophrenic group, the following brief clinical history is quoted:[4]

CASE 1.—(Patient 5, Table I.) Dan entered the hospital at the age of 7 because of temper displays, persistent enuresis, and physical attacks upon younger children. His physical condition was excellent.

When permitted, Dan preferred to wander away from any group with which he was playing and enjoyed roaming about in the woods by himself (*seclusiveness*). When attempts were made to dissuade him from these activities, he became sulky, pouty, glared at the supervisor, and muttered under his breath (*irritability*). During school hours he gazed into space and during leisure periods his attention seemed far from his surroundings (*daydreaming*). Dan was frequently observed striking and holding awkward postures. He growled like an animal when alone and showed little obvious emotional reaction to situations and events which should have pleased him (*bizarre behavior*). He seemed to enjoy few activities beyond being alone, daydreaming, and talking to himself (*diminution in number of personal interests*). On the rare occasions when he sought the company of other children he preferred to be with those much younger than himself and often sought attention from them

by using obscene language in a very immature fashion (*regressive nature of personal interests*). When praised he blushed profusely and seemed obviously embarrassed but he cried easily at the slightest scolding (*sensitivity to comment and criticism*). He rarely engaged in the boisterous games common to boys of his age and walked slowly instead of running (*physical inactivity*).

Although this case illustrated the presence of examples of all eight cardinal children's schizophrenic traits, it must not be inferred that a diagnosis depends on so complete a picture in every instance. The group of traits represents rather a symptom-complex of specific observable behavior phenomena which may distinguish schizophrenic and schizoid children from those with other emotional and behavior problems. Table I illustrates the presence or absence of each of the eight traits in the fourteen children clinically diagnosed as schizophrenic in this first group.

TABLE I. BEHAVIOR TRAITS PROMINENT IN FOURTEEN SCHIZOPHRENIC AND SCHIZOID CHILDREN BETWEEN 7 AND 13 YEARS OF AGE

	PATIENTS' NAMES AND NUMBERS													
TRAITS	ALICE 1	BEATRICE 2	CHARLES 3	GWEN 4	DAN 5	ED 6	FRANK 7	HARRY 8	IRA 9	JACK 10	KARL 11	LEN 12	MARY 13	NICK 14
Seclusiveness	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Irritability	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Daydreaming	*	*	*	*	*	*	*	*	*	*	*	*	–	–
Bizarre behavior	*	*	*	*	*	*	*	*	*	*	*	*	–	–
Interests—diminution	*	*	*	*	*	*	*	*	*	*	–	–	–	–
Interests—regressive	–	*	*	*	*	–	*	*	*	–	–	–	–	–
Sensitivity	*	–	–	*	*	*	–	*	–	*	*	*	*	*
Physical inactivity	*	–	–	*	*	*	*	*	*	*	–	–	*	–

It will be noted that seclusiveness and irritability when seclusive activities were interrupted were present in all fourteen children. Because of this, it may at least be assumed that a combination of these two traits is a basic characteristic of this particular symptom-complex. Many of the other individual traits noted may have been secondary to these. In the original communication it was suggested that irritability upon interruption of seclusive activities may well be a measure of the degree to which each child desired to be alone and pursue his solitary way. One does not become irritated, angry, or negativistic when pursuing some object unless that object has meaning and is really desired. This accentuates the fact that each of these schizophrenic children was not merely apathetic and indifferent to others about him but had a strong desire or "drive" *not to share* in their activities.

The children in this original group were between 7 and 13 years of age. In searching for early evidence of psychoses it has subsequently seemed important to see whether the same traits were prominent in younger psychotic children. Accordingly, the case records of all patients admitted to the Bradley Home over a period of fifteen years for whom a diagnosis of schizophrenia was suggested were

reviewed. Out of a total of 905 individual children admitted there were thirty-nine under 13 years of age for whom a diagnosis of schizophrenia seemed plausible. To further evaluate the prominence of the eight characteristics previously noted as earliest symptoms, the five youngest patients in the entire group were selected for particular study. These little children ranged from 39 to 48 months of age on admission. The occurrence of the important schizophrenic characteristics in these five children has been tabulated in Table II.

TABLE II. BEHAVIOR TRAITS NOTED IN FIVE YOUNGER SCHIZOPHRENIC CHILDREN BETWEEN 3 AND 4 YEARS OF AGE

TRAITS	PATIENTS' NAMES AND NUMBERS				
	OLIVER 15	PRISCILLA 16	RALPH 17	SAM 18	TOM 19
Seclusiveness	*	*	*	*	*
Irritability	*	*	*	*	*
Daydreaming	–	–	–	*	*
Bizarre behavior	*	*	*	*	*
Interests—diminution	–	–	–	*	*
Interests—regression	*	*	–	–	–
Sensitivity	–	–	*	–	–
Physical inactivity	*	–	–	*	*

The apparently essential characteristics of seclusiveness and irritability when seclusiveness was interrupted were symptoms common to all five of these younger children, whereas the presence of the other manifestations was possibly less consistent than in the older group. At this earlier age range the particular actions whereby the traits were expressed often varied from what was seen in the more mature and well-developed older children. The following case reports illustrate how some of these manifestations may display themselves in very young schizophrenic children.

CASE 2.—Ralph (patient 17, Table II) was admitted to the hospital nursery school at the age of 3 years and 7 months because of minimal speech development, lack of interest in the activities of others (progressively noticeable for the previous six months), and hyperactive negativistic behavior of gradually increasing intensity. His physical and clinical laboratory status were not abnormal.

Ralph showed no interest in the other children in the nursery school nor in their activities. He spent all of his time in imaginative solitary play *(seclusiveness)*. He cried in a frustrated manner whenever his own play was interrupted *(irritability)*. If reprimanded he would strike himself. On other occasions he laughed spontaneously and heartily when no external stimulus was evident *(bizarre behavior)*. He overreacted to any correction, striking himself as mentioned and occasionally apparently attempting to dominate the attention of adults in a rather planful fashion *(sensitivity to comment and criticism)*. There were no extreme evidences of *daydreaming*. His personal interests, though solitary, were fairly wide and adequate for his age and development. His motor activity was that of the usual boy of his age.

Psychometric examination was not feasible with this child. However, his ability to care for all the details of his personal hygiene, his familiarity with the varied and stimulating complicated nursery school schedule, and the particularly planful manner in which he tried to attract the attention of adults suggested potentially adequate intelligence.

Most conspicuous at first glance were his lack of speech, his carefully planned attempts to attract attention, and his apparent fear of new situations. However, over a period of thirteen months' observation, solitary activities and lack of interest in other children and their play seemed dominant and led to a diagnosis of schizophrenic psychosis.

CASE 3.—Sam (patient 18, Table II) was admitted to the hospital at the age of 3 years and 10 months because of loss of speech which he had supposedly acquired prior to 16 months, progressive faliure to respond to orders and direction, conspicuous avoidance of people, and unusual interest in printed letters and symbols of all sorts. Repeated physical examinations were negative. The usual hospital laboratory studies were noncontributory.

In the hospital nursery school, Sam showed no interest in the person or activity of other children or adults, paid no attention to suggestions which were given to the group, and was extremely preoccupied with his own solitary play *(seclusiveness)*. When this play was interrupted, particularly by any direct suggestion to him, an excessive temper reaction was provoked and he would strike his head against the floor *(irritability)*. At times he appeared preoccupied with his own thoughts (though not obviously busy) and in spite of attractive nursery activities about him seemed to be *daydreaming*. He was avidly interested in letters and other symbols of printed form, signs, books, scraps of writing, and children's lettered blocks, and followed out a ritual of bowing his head over such materials *(bizarre behavior)*. His only real interest in life seemed to be these printed objects *(diminution of personal interests)*. Though limited in amount, these interests could hardly be regarded as *regressive* for a child of his age. No evidence of *sensitivity to comment or criticism* was noted. He was slow in all his motions and rarely gave the impression of being active and alert as is usually seen in the nursery school *(physical inactivity)*.

This boy's superior ability in using a pencil, in printing, in recognizing and arranging symbols, and his self-sufficiency in dressing seemed adequate evidence of potential normal intelligence although all attempts at psychometric evaluation failed.

Almost as striking as his exclusively solitary preoccupation with letters and figures was his lack of speech in contrast to well-developed finger dexterity. On the basis of several months' observation, the completely self-centered, inwardly motivated features of Sam's life seemed the basis of these symptoms and led to the diagnosis of a psychosis, presumably schizophrenia.

CASE 4.—Tom (patient 19, Table II) was admitted to the hospital nursery school at the age of 4 years because he had progressively withdrawn from the activities of his home, had failed to develop speech, and was extremely concerned about what he ate, limiting this to a very few foods.

In the hospital this boy disregarded all suggestions made to the group, rarely showed interest in what went on about him, either among children or adults, and preferred to sit alone rocking back and forth and vocalizing in unintelligible sounds *(seclusiveness)*. When any attempt to direct him from these activities was made he cried bitterly *(irritability)*. Frequent episodes of unprecipitated laughter were noted and his general air of preoccupation suggested *daydreaming*. An infinite number of *bizarre activities* included grimacing with his hand held before him, and vocalizing starting with a low voice which he rapidly raised to a loud shout. He often seemed particularly interested in doors, locks, and gates. His food habits showed a fluctuating interest in special items, what he actually ate being usually chosen on the basis of color or texture rather than because of their taste or quantity. Although he occasionally showed fleeting attention to nursery school activities, he would always return to his own solitary fantasy life *(diminution of interests)*. There was no definite evidence of *regressive*

interests aside from these bizarre activities of undeterminate maturation level. He showed no evidence of *sensitivity to comment and criticism*. He stood about or sat so much during his solitary activities that he gave the impression of a much less *physically active* boy than others of his age group.

Formal psychometric examination could not be carried out with any degree of reliability. However, Tom's keen recognition of foods of certain texture or color, the ingenious methods he used to secure them at the table, and his self-sufficiency in caring for his dressing and similar needs all suggested potentially normal intelligence.

His bizarre activities, particularly those relating to his feeding habits, were his most obvious symptoms. Complete lack of speech was almost as conspicuous. Over an 11-month period of observation, the extremely self-absorbed, apparently internally motivated nature of all his behavior was sufficiently impressive to lead to a diagnosis of schizophrenic psychosis.

In what has been said so far an attempt has been made to demonstrate that the basic elements of the behavior of schizophrenic children can be observed and can be recorded in nontechnical language by observers who need not be experts provided they are relatively free of bias and prejudice. These behavior characteristics seem to apply to psychotic children down to very tender ages. Whether or not they are evidences of psychosis in its earliest developmental stages, they are certainly evidences of psychosis in the very early life stages of individual psychotic patients.

EARLIER EVIDENCES OF MALADJUSTMENT

In an attempt to search back further into the lives of children who were later thought to be psychotic, the early histories of all thirty-nine schizophrenic children admitted to the Bradley Home over a fifteen-year period were carefully reviewed. Thirty-two of the histories contained specific descriptions of behavior and development in infancy and earliest childhood. In the remainder this information was lacking so that these seven histories were discarded for the purposes of this part of the study. Evaluating the information obtained from the thirty-two reliable early histories, it must be noted that the material was taken from the usual hospital records and not obtained as any part of a research project. Since there were no siblings in this series, in informants were thirty-two different sets of parents and relatives. Moreover, the histories were obtained by a number of different staff physicians over a period of several years. Any points of agreement in data obtained from the histories of this many children under the variables which these conditions impose may obviously be of some clinical significance.

Age of Earliest Noted Maladjustment.—In searching for specific statements to indicate the earliest age at which evidences of maladjustment had come to parents' attention it was striking that in twenty-nine out of the thirty-two children definite evidence of this sort had been present before 2 years of age. Thirteen of these children were recalled as having presented definite problems at ages which were specifically recalled as "before one year," "at 16 months," "before

2 years," etc. In the remaining nine cases "infancy" only was specified. From the nature of the complaints in the entire group and the way in which the information was obtained, two years seems a reasonably conservative upper limit of what was implied when "infancy" was mentioned and not qualified by more specific dates.

Nature of Earliest Noted Maladjustments.—The precise behavior symptoms noted in these hospital histories as occurring during the first two years of life were quite diverse. For some, isolated symptoms, and for some a variety were reported. The positive statement most frequently made indicated that a child had shown a lack of interest in his surroundings, particularly in other persons, during this early age period. This was reported for twelve children.

Next to this lack of interest the most common observation was retardation or failure of speech development, occurring in eight children. In six others in whom speech had apparently been developing normally, it disappeared during the infancy period. Thus a total of fourteen children gave some evidence of disturbed speech development.

Nine children had presented feeding problems of various sorts, some extremely severe but none particularly characteristic of the group as a whole.

Conspicuous hypermotility and hyperactivity were distinctly recalled by the parents of six children.

These symptoms of diminished interest, retardation, or interruption of speech development, feeding problems, and increase of motor activity were by no means all the early signs of maladjustment reported. None of the great variety of others, however, occurred in sufficient frequency to warrant special mention.

LONG-TERM STUDIES OF INDIVIDUAL CHILDREN

The entire psychiatric literature contains but two detailed long-term studies of children who were thought to be schizophrenic in early childhood and for whom details of early development in the form of notes were kept in diaries by their parents.[5, 6] It has been the writer's privilege to have access to one of these documents which has previously been edited and published.[6] A brief résumé of the outstanding features of this girl's early development may be of interest.

CASE 5.—Gwen (patient 4, Table I) was an only child. A personal and professional acquaintance by the author with her parents and numerous relatives has revealed no serious abnormalities of parental maladjustment or familial defect. The father was of superior education and enjoyed enough leisure time during his daughter's early childhood to keep a detailed diary starting at a considerable period before any abnormality or serious problem was even suspected.

After an apparently uneventful pregnancy, birth, and early development Gwen, at 8 months of age, began to show a violent dislike to having any other child in the play-pen with her. At this same age it is recorded that she "smiled less than other children." At 9 months she was noted to scream when neighborhood children merely looked into her carriage. At one year of age she would shut her eyes and turn away from any strangers. At 18 months she seemed contented only when playing by herself.

Gwen's speech development was somewhat retarded. She was 17 months old before she was heard to speak her first word. At 2 years she used single words only. When she was 3 years old, she was said to be talking in a very "parrot-like" fashion.

Details of Gwen's subsequent development have been reported elsewhere, but following her admission to the Bradley Home her outstanding characteristics were described as follows:

She kept away from other children whenever possible and when physically close to them did not converse. She was frequently seen standing behind the door of her room muttering and often lay montionless on her bed with her eyes half closed and a rapturous expression on her face *(seclusiveness)*. If these solitary activities were interrupted, she would scowl and vehemently express her displeasure *(irritability)*. She paid little attention to her work in school, often sitting for long periods with eyes closed or gazing into space while otherwise unoccupied *(daydreaming)*. There was a great deal of *bizarre behavior*, examples of which were urinating out of the window or into her shoes, defecating in her clothes locker, frequently grimacing, often refusing to respond to questions, and at every opportunity assuming unusual postures such as lying on the floor with legs uplifted and underclothes exposed regardless of who might be observing her. Her *interests were diminished*, and although she rarely paid attention to what was going on about her, conversation revealed that she missed few details. Her bizarre exploratory activities, considerable masturbation, and finger play suggested that her *interests were regressive* in nature. If she were corrected or scolded, she sometimes cried and usually reminded members of the staff that no one liked her. In addition, she expressed ideas that adults whom she could see but not hear were being critical of her and in many other ways appeared *sensitive to comment and criticism*. She spent so much time alone and so often refused to participate in other children's games that the impression she gave was one of *physical inactivity*.

There appeared unexplained mood swings and variation in interest and activity from time to time, but over a long period of hospitalization no fundamental change or improvement was noted. Gwen's preoccupation with her own fantasies and her disdain for any of the activities of others remained quite constant and, when supplemented by the other details mentioned, led to a diagnosis of schizophrenic psychosis at the age of 8 years.

This brief résumé of a voluminous long-term study is used to illustrate the evolution of problems present in infancy to the symptom-complex of behavior traits mentioned above. There is an obvious need for many more such studies if we are to understand adequately the early evidences and development of psychoses in children.

COMMENT

These attempts to describe behavior which may be characteristic of schizophrenic children were originally motivated by a desire to secure from the study of patients themselves information which would remove from the diagnosis of childhood schizophrenia the inconsistencies with which conflicting psychological theories and the dependence on clinical intuition had previously surrounded it. While the traits enumerated are clearly at a descriptive level only, the importance of observation and description as aids in diagnosis needs no justification. In the early differential diagnosis of a child's behavior disorder, the first impressions received by the physician are derived from what parents and others tell him of the patient's behavior. They are usually next supplemented by what the physician himself may observe. If both the history and symptoms suggest extreme seclusive tendencies in combination with several of the other eight traits that have been described, and are supported by a story of maladjustment going back into earliest childhood years, the possibility of schizophrenia must be considered and more complete psychiatric study advised.

It is beyond the scope of this communication to discuss in any detail the possible causes of schizophrenic reactions in children. More comprehensive re-

views[3, 7] indicate that no appreciable proportion of reported cases can be traced to any specific abnormalities of heredity, the prenatal state, birth and medical history, life experiences, intellectual capacity, or recognizable physical characteristics. That the specific reaction can appear so early and is usually preceded by definite though less specific evidences of inability to meet the demands of life even in infancy suggests that a constitutional predisposition is the basic handicap. This naïvely expressed concept is not as impractical as it may sound, since it allows us to recognize that physical or emotional trauma only precipitates or intensifies the pathologic reactions to which the patient is intrinsically predisposed. In other words, the many suggested causes of schizophrenia (ranging from parental overprotection and unstable or dominant mothers to early injury of the nervous system and endocrine imbalance) may intensify symptoms to the point of attracting clinical attention but should not necessarily be considered the particular objects of treatment in the case of every schizophrenic child.

Obviously not all seclusive children are potentially schizophrenic nor is all infantile maladjustment the precursor to psychosis. The intensity and persistence of reactions such as those described are quite as important for diagnostic purposes as their quality. Mild or brief episodes of schizoid behavior may be noted at times of stress or illness in some children whose previous and subsequent adjustment is entirely adequate. A definite and serious diagnosis is justified only upon repeated or prolonged observation of significant reactions either in a variety of situations or in a setting where the child is temporarily free from external complicating factors.

Since schizophrenia in children appears to be a way of life rather than a disease, its existence is not incompatible with that of other handicaps such as mental deficiency, epilepsy, or cerebral palsy, to mention only a few coexisting conditions that have come under the writer's observation.[3]

Treatment and prognosis are further complex subjects outside the province of this presentation. Therapy is basically a problem of eliminating or reducing factors which intensify the child's fundamental maladjustment.[3, 8, 9] It is essentially a psychiatric problem, since modifications of parental attitudes, alleviation of secondary symptoms, and special educational programs are involved. Ultimate prognosis depends both upon the degree to which remediable factors can be successfully brought under control and the degree to which constitutional predisposition is present.[3, 10] The latter is generally assumed to be severe if schizophrenia is apparent at an early age. While no invariable course and outcome can be predicted, a well-substantiated diagnosis of schizophrenia in childhood carries with it a serious prognosis.

SUMMARY

In a study of schizophrenic children in the controlled environment of a children's psychiatric hospital, eight behavior characteristics were noted to distinguish these patients from other seriously maladjusted children. These traits were diagnostically significant as early as the fourth year. A review of

the early histories of schizophrenic children revealed evidence of maladjustment before 2 years of age in most instances. The significance of these early evidences of psychosis in young children is considered.

REFERENCES

1. Bradley, C.: Psychoses in Children. In Lewis, N. D. C. and Pacella, B. L. Modern Trends in Child Psychiatry, New York, 1945, International Universities Press, pp. 135-154.
2. Hinsie, L. E., and Shatzky, J.: Psychiatric Dictionary, New York, 1940, Oxford University Press.
3. Bradley, C.: Schizophrenia in Childhood, New York, 1941, The Macmillan Co.
4. Bradley, C., and Bowen, M.: Behavior Characteristics of Schizophrenic Children. Psychiat. Quart. 15: 296, 1941.
5. Tramer, M.: Tagebuch ueber ein geisteskrankes Kind. Ztschr. f. Kinderpsychiat. 1: 91, 1934; 1: 123, 1934; 1: 154, 1934; 1: 187, 1935; 2: 17, 1935; 2: 86, 1935; 2: 115, 1935.
6. Bradley, C.: Biography of a Schizophrenic Child. Nerv. Child. 1: 141, 1942.
7. Lutz, J.: Ueber die Schizophrenie im Kindesalter. Schweiz. Arch. f. Neurol. u. Psychiat. 39: 335, 1937; 40: 141, 1937.
8. Cottington, F.: Treatment of Schizophrenia of Childhood. Nerv. Child. 1: 172, 1942.
9. Rapoport, J.: Therapeutic Process in a Case of Childhood Schizophrenia. Nerv. Child. 1: 188, 1942.
10. Lourie, R. S., Pacella, B. L., and Piotrowski, Z. A.: Studies on the Progress of Schizophrenic-like Psychoses in Childhood, Am. J. Psychiat. 99: 542, 1943.

STREPTOMYCIN: A REVIEW

JOHN EHRLICH, PH.D.
DETROIT, MICH.

IT HAS been said that, whereas the discovery of penicillin was, in a sense, accidental, streptomycin came to light in the course of a premeditated and carefully planned search for just such a drug. Biologists, of course, had long noted the phenomenon of antibiosis, and an almost unbroken succession of laboratory workers and clinicians, stemming from Pasteur, have sought to exploit its implicit therapeutic possibilities.

Waksman of Rutgers University, long noted as a soil microbiologist, had undertaken, in the late 1930's, the onerous task of screening his microorganisms, new isolates as well as stock cultures, in a series of tests designed to uncover any cultures whose metabolic products might, after extraction and purification, meet the exacting requirements of clinicians. Several powerful new antibiotic substances came to light, but it was not until 1943 that his group found one that gave promise of meeting these requirements. An Actinomycete, apparently *Streptomyces griseus,* an inhabitant of garden soils, river muds, peat, and compost heaps, was found to produce a substance exhibiting powerful bacteriostatic activity, especially against many of the gram-negative pathogens not sensitive to penicillin. Among the more susceptible of these in agar-dilution tests were *Brucella abortus, Eberthella typhosa, Escherichia coli, Hemophilus influenzae* and *Hemophilus pertussis, Klebsiella pneumoniae, Pasteurella tularensis, Proteus vulgaris, Pseudomonas aeruginosa* (relatively resistant), and *Salmonella schottmuelleri.* In addition, a pathogenic human strain of *Mycobacterium tuberculosis* was found to be inhibited. Later in vitro tests added a number of additional pathogenic species, including *Bacillus anthracis, Brucella melitensis* and *Brucella suis, Corynebacterium diphtheriae, Neisseria gonorrhoeae* and *Neisseria intracellularis (meningitidis), Pasteurella pestis, Proteus ammoniae, Salmonella enteritidis, Shigella paradysenteriae, Streptococcus faecalis* (relatively resistant), and *Actinomyces bovis.* Penicillin-sensitive gram-positive aerobes were not notably affected, and anaerobes, fungi, and viruses not at all. When extracted and partially purified, the active substance was found to be encouragingly stable and relatively nontoxic for laboratory animals.

The discovery was announced in January, 1944, together with information on culture media and a method for extraction and concentration of streptomycin from culture filtrates. Before the end of 1944, transplants of the active cultures (not all isolates proved to be equally productive) were distributed to numerous industrial laboratories, where the formidable resources of equipment, man power, and "know-how," only recently marshalled for penicillin, were concentrated on the more difficult task of developing workable production methods, for it was realized by the Rutgers group that without the help of industry it

From the Research Laboratories of Parke, Davis & Company.
Presented before the Fifteenth Annual Meeting, American Academy of Pediatrics, Pittsburgh, Pa., Feb. 24-27, 1947.

might take years to produce sufficient material for the crucial clinical tests on which the future of this apparently safe and powerful antibacterial substance would necessarily depend. In less than a year streptomycin was in limited production, further animal studies were completed, and clinical trials were under way. Shortly thereafter, eleven manufacturers contributed nearly one million dollars to the National Research Council for a comprehensive program of clinical trials under the supervision of Dr. Chester S. Keefer. It soon became apparent that Waksman's hopes were destined to be at least partially sustained. By 1946, the limitations of this new drug were fairly well defined, specifications were drawn up by military and civilian control agencies, and its probable therapeutic value was forecast.

Production, which had been about 3 kg. during September, 1945, increased to almost 40 kg. for May, 1946, and reached slightly over 200 kg. for December, 1946. Certification of individual lots for civilian use is not legally required at present, but all members of the industry have voluntarily agreed to submit samples of each lot to the Food and Drug Administration before release.* On Sept. 1, 1946, the Civilian Production Administration designated 1,652 hospitals to serve as regional depots for the controlled commercial distribution of streptomycin for civilian treatment. By November, the supply had increased sufficiently to justify relaxation of controls; since that date, hospitals and sanatoriums have been permitted to order the drug direct from suppliers of their choice. The Civilian Production Administration still allocates domestic and export release quotas from each manufacturer or supplier, and the Office of International Trade of the United States Department of Commerce controls distribution of export quotas among various exporters. But since Dec. 1, 1946, domestic sale, within allocation, has not been restricted and is now handled through normal trade channels. It is hoped that additional manufacturing facilities now under construction will increase the supply of streptomycin sufficiently within six months to justify lifting of the present allocation system. During recent months, the cost of the drug has been halved twice with the result that, weight for weight of equivalent pure material, it is now as cheap as penicillin.

Streptomycin is an organic base, soluble in water and insoluble in most organic solvents. It may be considered as related to sugars (in contrast to penicillin which is more related to amino acids). From partially purified hydrochloride or sulfate salts it has been possible to prepare three crystalline salts, the helianthate, and the double salts reineckate sulfate and trihydrochloride-calcium chloride. A derivative, dihydrostreptomycin, has also been prepared by catalytic hydrogenation of streptomycin hydrochloride or the trihydrochloride-calcium chloride double salt. The calculated formula for streptomycin is $C_{21}H_{39}N_7O_{12}$. As a result of experimental work by numerous organic chemists, the general structure of the molecule is now well defined. The molecule has been split into two components, streptidine and streptobiosamine. The streptidine

*On March 10, 1947, President Truman signed the streptomycin amendment (H. R. 2045) to the Federal Food, Drug, and Cosmetic Act. This amendment places streptomycin on the same basis as penicillin, including the requirement that samples of each manufactured lot be submitted to the Food and Drug Administration and certified by the administration before the lot is released for distribution.

portion is a diguanido inositol and the streptobiosamine is made up of an unnatural (levo) optical isomer of N-methyl glucosamine and a hitherto unknown branched-chain hexose (streptose or streptonose) bearing two aldehyde groups. The streptidine and streptobiosamine are joined in the parent streptomycin by a glycoside linkage of the streptonose portion of streptobiosamine to one of the oxygen atoms of streptidine. One suggested chemical assay method is based on the formation and colorimetric determination of maltol (a previously known compound) from the streptonose portion of the intact molecule upon treatment with alkali. On the basis of present knowledge, the molecule can be varied only at the aldehyde group in the middle fragment. Oxidation to the organic acid destroys its activity. Reduction to the aldehyde increases the alkali stability of the compound and does not materially change its in vitro activity. Suffice it to say that a structure so complex and unfamiliar offers even less hope than does that of penicillin for artificial synthesis.

Consequently, we are dependent for streptomycin on natural biosynthesis. Being an aerobic organism, *S. griseus* must be cultivated aseptically on the surface of suitable liquid media or throughout the medium in large culture tanks through which large volumes of sterile air are bubbled under controlled conditions. The organism produces relatively minute amounts of streptomycin—at present not much more than 0.0001 Gm. per milliliter of the culture liquid. This precious fraction must be extracted and purified by an exacting procedure involving filtration, adsorption, elution, concentration, and desiccation; inevitably, much is lost in the process. The final product is an almost colorless powder, sterile, free of pyrogenic substances, free or almost free of histamine-like activity, safe for injection, and remarkably stable. Since the free base is unstable, the streptomycin is present in the form of a salt, usually the hydrochloride or the sulfate. The potency of these preparations is at least 300 μg. of pure streptomycin base (or "S units") per milligram of powder. Since a milligram of either of these salts, when pure, contains approximately 800 μg. of streptomycin base, the powders now available contain at least 40 per cent of active streptomycin base. The powder is readily soluble in water; when reconstituted with sterile, pyrogen-free water in a concentration of 100 or 200 mg. of streptomycin base per milliliter, it forms a clear solution of pH 5.0 to 7.0. Solutions for injection may be prepared either with water or with physiological saline solution.

Throughout the manufacturing process, progressive concentration of the active material is followed closely by means of potency assays. Rapid and precise chemical methods are being sought, but at present two biologic methods are in common use, an agar-diffusion method employing a strain of *Staph. aureus* or more commonly *Bacillus subtilis*, and a turbidimetric method employing a noncapsulated strain of *K. pneumoniae*. Assays of pharmacologic and clinical samples for following streptomycin concentration in body fluids have been performed by Fleming's slide-cell method with *Bacterium megatherium* or by a serial-dilution endpoint method with broth cultures of *K. pneumoniae* or *Bacillus circulans*. In all methods, the samples are compared with corresponding dilutions of a streptomycin preparation of known potency, based on the working

standard distributed by the Food and Drug Administration from pooled lots of streptomycin sulfate contributed by most of the manufacturers.

Although the in vitro sensitivity of an organism cannot, unfortunately, be taken as an infallible guide to its sensitivity within the body, it is generally agreed that the infecting organisms should be isolated from candidates for streptomycin therapy and that the streptomycin sensitivity of the organisms should be determined both before and throughout the course of treatment. The value of such in vitro tests is now known to be affected, in part at least, by their character, for it has been shown that the in vitro sensitivity of an organism to streptomycin is influenced by many factors, including age of culture, concentration of organisms, growth phase of the culture, and constituents of the medium used.

When therapeutic blood levels are sought, streptomycin can be injected by the common parenteral routes. Since adequate blood levels can be established in less than two hours following intramuscular administration, there is little to recommend the more speedy intravenous route (except in fulminating cases of bacteremia) or the more painful subcutaneous route. Blood concentration has been found to be generally proportional to the size of the dose, a sustained level of 10 μg. of streptomycin base per milliliter of blood being attained with 0.6 Gm. a day, and a daily dose of 1.5 to 2.0 Gm. being found necessary to raise the blood level above 16 μg. per milliliter. Serum levels of 32 μg. per milliliter have been maintained with daily parenteral administration of 3 Gm. Absorption is more rapid from saline than from peanut oil and beeswax. Following intramuscular injection, streptomycin is readily distributed throughout most of the body fluids and has been found in fetal cord blood and amniotic fluid. Much of it concentrates in the kidneys, whence 50 to 75 per cent of the total amount administered is excreted with the urine within twenty-four hours. It is thus possible to maintain drug levels in excess of 100μg. of streptomycin base per milliliter of urine by parenteral dosage at a rate considerably less than 1 Gm. a day. A small portion is also excreted in the bile. Streptomycin does not readily diffuse into the cerebrospinal fluid of normal persons; but when administered parenterally to patients with meningitis, amounts sufficient to check growth of susceptible bacteria may reach the cerebrospinal fluid after repeated injections. Larger intracisternal levels can be obtained by supplemental intrathecal injection of 25 to 50 mg. a day. Oral administration is contraindicated where systemic drug levels are required, because no appreciable amounts of streptomycin pass through the gastrointestinal wall; likewise, parenteral administration is valueless in the treatment of gastrointestinal infections. However, since the drug retains its activity in the gut, oral administration of 2 to 4 or 5 Gm. per day is strikingly effective in reducing or obliterating the fecal flora and thus, apart from its curative effect in some cases of bacillary dysentery, offers a useful sanitation procedure prior to operation on the colon. Similarly, although streptomycin is not absorbed to any appreciable extent through normal lungs, inhalation of nebulized streptomycin provides a valuable supplement to penicillin in preparation for pleural surgery as well as in the treatment of some cases of chronic pulmonary suppuration. Solutions containing $\frac{1}{10}$ to 1 Gm. may

be injected into the pleural or peritoneal cavity. Dry mixtures with lactose (250 mg. per gram) or aqueous solutions (50 to 100 mg. per milliliter) may be applied topically.

While it is true that even relatively pure streptomycin sometimes produces unpleasant side reactions, particularly when massive doses are administered over long periods of time, yet the drug is remarkably free of toxicity and, excepting penicillin, is safer than any chemotherapeutic agent yet found. Certain patients exhibit familiar types of drug sensitivity, including pain and tenderness at local site of injection, headache, fever, skin eruptions, tachycardia and fall in blood pressure, paresthesias about the face, and flushing of the skin. Those under prolonged courses of treatment for stubborn inaccessible infection such as tuberculosis eventually exhibit eighth-nerve disturbances; vertigo and tinnitus disappear when treatment is suspended; deafness is apparently often irreversible, but is more or less readily compensated. In short, streptomycin is hardly indicated where cheaper or less irritating agents will serve equally well, but may be used without hesitation where the prognosis is poor or where other means of treatment are inadequate, and especially in cases where laboratory tests on the isolated culture show the infecting organism to be streptomycin sensitive.

Streptomycin has been found to evoke a multifold increase in resistance to its action on the part of many organisms, not only in vitro but unfortunately also in vivo. This increase in resistance may be brought about in part by the action of serum and of other factors within the body, in part by selective action of the drug, resulting in unhampered multiplication of relatively resistant individuals and concomitant elimination or possibly mutation-like alteration of the more sensitive individuals. Hence, as with the sulfonamides and penicillin, it is safest and most effective in the treatment of infections which will respond quickly to massive, briefly sustained medication.

Where streptomycin therapy has failed, at least one of five causes has been assigned: (1) the organism was not sensitive to streptomycin; (2) dosage was inadequate; (3) the organism became resistant during treatment; (4) the predominant species of infecting organism changed during treatment; (5) infection became localized in an area inaccessible to streptomycin. It is hardly necessary to point out that bacteriologic studies could have prevented or at least directed prompt attention to each of the first four causes of failure.

Although clinical experience is now accumulating rapidly, it is still too early for a full evaluation of streptomycin, and this is especially true of relatively inacessible chronic infections such as leprosy and tuberculosis. A study of ten patients at the National Leprosarium just completing a seven-month course of treatment, five of them with sulfones and five with sulfones plus streptomycin, indicates that while streptomycin produces encouraging results, its cumulative toxicity when administered in large and continuous dosage (1 or 2 Gm. a day) is such that, alone, it will probably not become the drug of choice in leprosy. Although streptomycin is the most dramatically efficacious chemotherapeutic agent yet found for the treatment of tuberculosis, permanent benefit in long-standing infections, and in meningeal or miliary forms of the disease

appears doubtful. Its greatest usefulness will probably be as an adjuvant in the treatment of those early forms of tuberculosis likely to be permanently benefited by one to two months of streptomycin treatment; that is, early, acute, progressive, exudative forms of pulmonary tuberculosis with or without thin-walled cavities, and ulcerating lesions of the larynx, hypopharynx, tracheobronchial tree, and sinus tracts. The daily dose has usually been between 1.5 and 3 Gm. While "the place of streptomycin in tuberculosis therapy has not been fully determined," it appears, in the words of the Mayo clinicians, "to have a very great usefulness which is much more likely to supplement than to supplant the proved effective standard methods of treatment."

Streptomycin therapy appears to be the best treatment available for tularemia (¼ to 1 Gm. daily for five to seven days) and for mild or moderately severe meningitis due to *H. influenzae* and to several of the other commonly encountered gram-negative organisms. For influenzal meningitis, the suggested daily dose is ½ to 1 Gm. intramuscularly, plus 25 to 50 mg. intrathecally, for five to seven days. Streptomycin has been found effective in children against severe influenzal meningitis of types other than b when supplemented with sulfadiazine, and against severe type b influenzal meningitis when supplemented with rabbit antiserum as well as sulfadiazine. Respiratory and other infections with *H. influenzae* have also responded satisfactorily.

Streptomycin is indicated for gram-negative bacteremias (2 to 4 Gm. daily for five to ten days) and for many heretofore resistant infections of the urinary tract (1 to 3 Gm. daily for five to ten days), especially those due to proved streptomycin-sensitive strains of *H. influenzae, K. pneumoniae, P. vulgaris, P. ammoniae, Ps. aeruginosa, Esch. coli, Aerobacter aerogenes,* and *N. gonorrhoeae.* To succeed in such urinary-tract infections, urination should be unimpaired, the urine should be alkalized, and marked benefit should result within three days. Many cases of gram-negative peritonitis, Friedländer's pneumonia, liver abscess, cholangitis, heart-valve invasion, chronic pulmonary infection, and empyema due to organisms of demonstrated streptomycin sensitivity have responded well to streptomycin therapy (usually 2 to 4 Gm. daily for five to ten days). Army surgeons have obtained excellent results with streptomycin applied directly to the external ear, to pleural cavities, and to brain infections. The place of streptomycin in the treatment of various enteric infections is still in doubt, although many cases of bacillary dysentery have improved under oral streptomycin therapy, usually supplemental to parenteral administration.

Its value in typhoid fever, salmonella infections, brucellosis, and cholera is questionable, but its attempted use may be justifiable in some severe cases (3 to 5 Gm. daily for ten to fourteen days). Streptomycin is ineffective in malaria and in infections due to Rickettsiae, viruses, Clostridia, and fungi.

These remarks have been necessarily discursive and superficial. If they have helped to outline the background and nature of this very new antibiotic substance and to indicate its already established and probable future role in the chemotherapeutic armamentarium, they have served their intended purpose.

OSSEOUS CONGENITAL SYPHILIS: EFFECTS OF PENICILLIN ON RATE OF HEALING

ALLAN J. HILL, JR., M.D., RALPH V. PLATOU, M.D., AND JOHN T. KOMETANI, M.D.
NEW ORLEANS, LA.

OSSEOUS congenital syphilis is a dynamic process which waxes and wanes as the infant grows older, and late complete healing may be expected even when early lesions are severe. Evaluation of antisyphilitic treatment for this self-limited process is impossible unless the natural history of untreated osseous syphilis is kept clearly in mind. The course of untreated osseous syphilis may be altered by several factors, of which the most important would seem to be the age of the fetus at time of infection and the adequacy of treatment of the mother. Although fetal infection may take place as early as the fifth month, it frequently does not occur until just before parturition, even when the mother has been infected much earlier.[1] Therefore, the duration of the fetal infection before appearance of osseous lesions[1] cannot be determined accurately. It has been stated[2, 3, 4] that evidences of active syphilis seldom develop in newborn infants of syphilitic women who have received moderate or large amounts of antepartum treatment; and osseous lesions, if present, disappear within a few weeks. When we assume that adequate maternal therapy is responsible for rapid healing of fetal osseous lesions, we must consider two factors: First, in infants subsequently proved to be syphilitic, osseous lesions are commonly absent during the first few weeks of extrauterine life.[5, 6, 7] Second, in the newborn infant, many minor osseous abnormalities roentgenographically compatible with syphilis, but actually secondary to other disturbances, may be of a transitory nature.[2, 5, 8, 9, 10] Caffey[11] has indicated the many pitfalls that may be encountered in an unequivocal roentgenologic diagnosis of osseous congenital syphilis.

McLean's[12] classification was adopted for this study. For purposes of statistical analysis an arbitrary weight of severity was assigned to each type. The authors assume full responsibility for these arbitrary criteria which, although they may be found wanting with further experience, do have some merit for current purposes.

Osteochondritis.—(Fig. 1.) *Type I* consists of a single thickened line of increased density at the end of the metaphysis. It is nonspecific and may be encountered in a wide variety of conditions which produce disturbances in growth of cancellous bone. Some of these are malnutrition, bacteremia, miliary tuberculosis, hemolytic disease of the newborn, acute leucemia in the infant, and

This report represents work done under contract recommended by the Committee on Medical Research of the Office of Scientific Research and Development, and Tulane University. Investigation is now being continued under the auspices of the United States Public Health Service, following termination of OSRD contracts.

From the Department of Pediatrics, Tulane University School of Medicine, and the Charity Hospital of Louisiana.

Presented before the Fifteenth Annual Meeting of the American Academy of Pediatrics, Pittsburgh, Pa., Feb. 24-27, 1947.

illness or injections of bismuth in the pregnant woman.[2, 5, 8, 9, 10, 11] Accordingly, a weight of one in our scale was assigned to this lesion. *Type II* is seen as a similar thickened transverse line of increased density but with a contiguous and shaftward transverse zone of diminished density. Type II may also be observed with disturbances in growth encountered in hemolytic lesions of the newborn, familial hemolytic anemia, bacteremia, and multiple birth injuries.[5, 8, 11] Thus, though relatively nonspecific, this lesion is presumably a more severe manifestation and was given a weight of 2. *Type III* appears as a deep zone of decreased density at the end of the shaft, with diminution or absence of the terminal shadow of increased density. It has also been associated with extremely rapid growth, congenital biliary atresia, injections of bismuth, and toxoplasmic encephalitis.[5, 8, 11] A weight of 2 was assigned to it. *Type IV* is almost certainly a reduplication of Type II, being composed of either doubled transverse

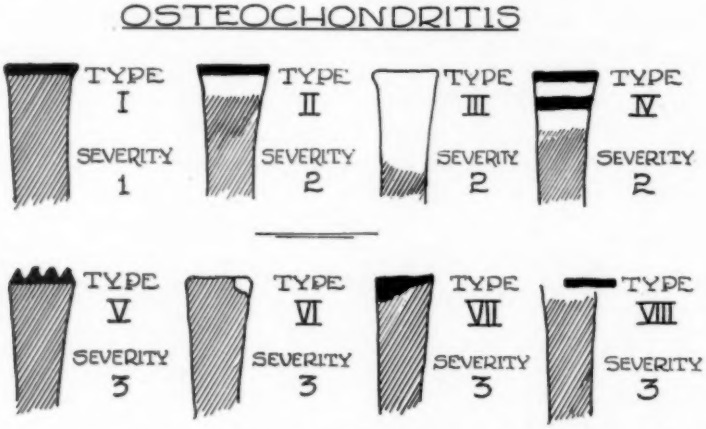


Fig. 1.—Diagrams to show types of osteochondritis observed and severity assigned to each (see text).

lines of increased density separated by a narrow band of diminished density or double alternating bands of increased and decreased density. Two widely separated periods of disturbances in growth or courses of bismuth injections can result in a similar appearance; it has also been seen in disseminated hematogenous tuberculosis.[2, 8, 11] Accordingly, a weight of 2 was assigned to this type. The remaining types of osteochondritis have been described only in osseous syphilis. Because of their specificity and also because the following types are usually seen only in the more severe forms of the disease, a grade of 3 was given to each: *Type V* is serration of the ends of the shafts, with "saw-toothed" metaphyses; *Type VI* is small foci of rarefaction or necrosis at the angle of the cartilage-shaft junction; *Type VII* is impaction through an area of osteochondritis; and *Type VIII* is horizontal displacement at the cartilage-shaft junction.

Osteomyelitis.—(Fig. 2.) *Type I* consists of circumscribed oval or circular areas of decreased density at the junction of metaphysis and diaphysis; *Type II,* of smaller areas of diminished density, usually seen in the shafts as slits or flat ellipses with the greatest axis parallel to that of the shaft; *Type III,* of bilaterally symmetrical areas of diminished density in the medial aspects of the proximal ends of the tibias, which erode the cortex immediately beneath the epiphyseal line (Wimberger's sign). These three were arbitrarily assigned grades of 2 in our scale. *Type IV,* fracture, may occur with any of the preceding, especially through Type II, and was indexed as grade 3. Although Types I and II may be encountered in acute pyogenic hematogenous osteomyelitis or multiple benign osseous tuberculosis,[11] they are also manifestations of fairly severe osseous syphilis. Whereas Type III may be pathognomonic of syphilis, it does not seem to appear more often in severe osseous syphilis than either Types I or II, and therefore received no greater weight. Although nonspecific, Type IV is associated with more extensive osteomyelitis and was weighted accordingly.

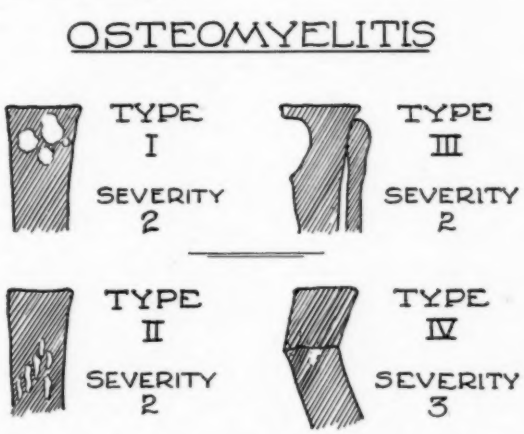


Fig. 2.—Diagrams to show types of osteomyelitis observed and severity assigned to each (see text).

Periostitis.—(Fig. 3.) *Type I* consists of a single line of periosteal elevation running nearly the length of the shaft but most pronounced near the middle; the underlying cortex and medulla usually appear normal. This type is encountered in many situations, as rapidly growing premature infants, malnutrition, traumatic periostitis of the newborn, and rickets.[2, 5, 9, 11, 12] Thus, a weight of only one was assigned. *Type II,* supportive and localized in nature, appears over cortical breaks or about regions of severe osteochondritis. For all practical purposes, it is very nearly identical with periosteal elevation seen with fractures, scurvy, osteomyelitis of pyogenic origin, or gonococcal periostitis.[11] Although relatively nonspecific, it is generally associated with more severe lesions and was given a weight of 2. *Type III,* essentially a multiplication

of Type I, consists of onion-skin periosteal thickening, variously designated as ossifying periostitis, hypertrophic periostitis, or periostitis of Pehu. Whereas this type is relatively unusual and is sometimes encountered with diseases other than syphilis,[13, 14, 15] it appears later than Types I and II and is probably a late manifestation of healing. In spite of these considerations, because it appears severe, it was arbitrarily assigned a weight of 3. In *Type IV*, the shaft is widened and the cortex is thickened in the early stages. Because this represents a stage of nearly complete healing, the weight assigned was only one. *Type V* signifies a localized thickening of the anterior tibial cortex. Though it may occur in other bones, trauma probably explains this characteristic localization and persistence (saber shin). We believe it has the same significance and deserves the same weight as Type IV.

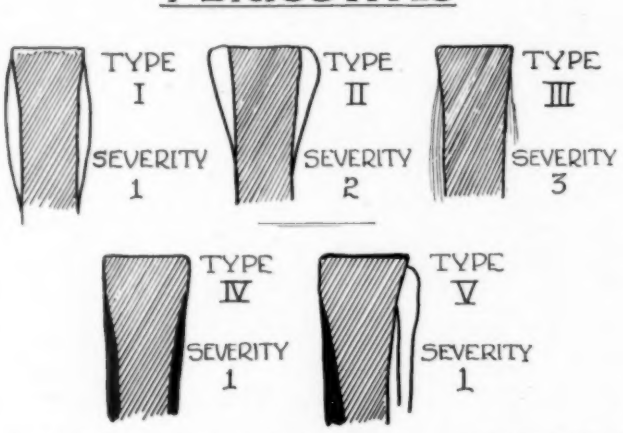


Fig. 3.—Diagrams to show types of periostitis observed and severity assigned to each (see text).

McLean[13] noted that the most common lesions developed in the first three months of life and considered those observed later to be residua or relapses. Data concerning such matters as the combinations of lesions, frequency of distribution in various bones, and variations with age, have been evaluated elsewhere[13, 16, 17, 18] and will not be worried further here. Just how much these osseous manifestations are influenced by associated vitamin deficiencies is difficult to determine. Certainly, pathologic evidence of rickets is far more common than radiographic,[13] and Levin[19] recently noted low levels for ascorbic acid in young syphilitic infants.*

In order to analyze the effect of penicillin on the rate of healing, it is necessary to know the behavior of untreated osseous lesions. The ideal group

*In only three infants of our series was the presence of either rickets or scurvy suggested by dietary history and clinical observations; characteristic roentgenographic evidence of these deficiencies, however, was lacking in all. Unfortunately, chemical studies were not made routinely. Since all infants received prophylactic amounts of vitamins C and D during and following treatment with penicillin, administration of these vitamins could conceivably have influenced rates of healing in a few.

for comparison would consist of a large number of untreated syphilitic infants observed radiographically at two-week intervals from birth to 6 months of age, and at longer intervals thereafter. Furthermore, not only should the accurate date of maternal infection be known, but also the maternal syphilis should have been untreated. For many obvious reasons, such crucial conditions are impossible to attain. Consequently, our control data were derived from 134 roentgenographic observations of ninety-eight infants made before penicillin therapy was started. Discontinuous data of this sort are imperfect but are the best we have available. Factual information concerning date of maternal infection was too meager for analysis. Socioeconomic circumstances were such that less than one-half of the mothers of infants studied had received antisyphilitic therapy of any kind prior to delivery. Only a small minority had received therapy which might be considered "adequate" according to accepted standards. In ninety-four prepenicillin observations made during the first six months of life, treatment had been administered during pregnancy in twenty-eight and was satisfactory[6] for only five. Infantile osseous lesions were severe in three and moderate in two of these. Whereas final analysis of effects of inadequate maternal therapy must await the cumulation of a larger sample, we doubt that subcurative amounts given the mother significantly influence the severity of lesions in the skeleton of her infant.

Tables I, II, III, and IV contain 134 roentgenologic observations in ninety-eight infants before treatment with penicillin. Combinations of osteochondritis, osteomyelitis, and periostitis (Table I) and the frequency of the various types of these (Tables II, III, and IV) are sufficiently obvious to require no further comment. An explanation is indicated at this point, however, concerning the estimation of severity. Suppose, for example, roentgenograms in an infant of 45 days disclosed osteochondritis of Types II and VII, osteomyelitis of Types I and III, and periostitis of Types I and II. By addition, the weight

TABLE I. PREPENICILLIN STATUS OF OSSEOUS CONGENITAL SYPHILIS IN NINETY-EIGHT INFANTS

DISTRIBUTION OF LESIONS BY MANIFESTATION AND AGE				
	AGE			
MANIFESTATIONS	1-90 DAYS	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	43	33	16	20
Number of observations	54	40	19	21
Normal	0	0	2	5
Osteochondritis only	7	2	1	2
Osteomyelitis only	1	0	0	0
Periostitis only	1	8	11	10
Osteochondritis and osteomyelitis	1	0	0	0
Osteochondritis and periostitis	13	5	4	1
Osteomyelitis and periostitis	2	3	1	2
Osteochondritis, osteomyelitis, and periostitis	29	22	0	1
SEVERITY				
$\bar{x}$*	6.759	6.550	2.895	2.524
S.D.$_x$	3.53	3.19	1.68	2.46
M.L.E.	3.56	3.23	1.73	2.52
S.E.$_{\bar{x}}$	0.49	0.52	0.41	0.56

*For explanation of symbols used in tables, see footnote in text.

TABLE II. PREPENICILLIN STATUS OF OSTEOCHONDRITIS IN NINETY-EIGHT INFANTS

RELATION OF TYPE TO AGE				
TYPE	AGE			
	1-90 DAYS	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	43	33	16	20
Number of observations	54	40	19	21
Absent	4	12	14	16
Type I	2	2	3	0
Type II	28	11	0	1
Type III	19	17	1	0
Type IV	1	2	1	2
Type V	11	4	0	1
Type VI	9	2	0	2
Type VII	1	3	0	0
Type VIII	3	1	0	0
SEVERITY				
$\bar{x}$	3.148	2.200	0.368	0.714
S.D.$_{\bar{x}}$	2.06	1.98	0.67	1.39
M.L.E.	2.08	2.01	0.69	1.42
S.E.$_{\bar{x}}$	0.28	0.32	0.16	0.32

TABLE III. PREPENICILLIN STATUS OF OSTEOMYELITIS IN NINETY-EIGHT INFANTS

RELATION OF TYPE TO AGE				
TYPE	AGE			
	1-90 DAYS	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	43	33	16	20
Number of observations	54	40	19	21
Absent	21	15	18	18
Type I	15	13	0	1
Type II	13	12	0	2
Type III	15	14	0	0
Type IV	7	2	1	0
SEVERITY				
$\bar{x}$	1.981	2.025	0.158	0.286
S.D.$_{\bar{x}}$	1.96	1.97	0.47	0.88
M.L.E.	1.98	2.00	0.48	0.90
S.E.$_{\bar{x}}$	0.27	0.32	0.11	0.20

TABLE IV. PREPENICILLIN STATUS OF PERIOSTITIS IN NINETY-EIGHT INFANTS

RELATION OF TYPE TO AGE				
TYPE	AGE			
	1-90 DAYS	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	43	33	16	20
Number of observations	54	40	19	21
Absent	10	2	3	8
Type I	35	28	4	4
Type II	22	7	1	1
Type III	1	16	8	5
Type IV	0	3	9	11
Type V	0	0	0	1
SEVERITY				
$\bar{x}$	1.611	2.325	2.368	1.524
S.D.$_{\bar{x}}$	1.21	1.42	1.50	1.65
M.L.E.	1.22	1.44	1.54	1.69
S.E.$_{\bar{x}}$	0.17	0.23	0.36	0.38

for osteochondritis is 5, osteomyelitis 4, periostitis 3, and the total severity equals 12. By this method the average severity of pre- as well as postpenicillin osseous syphilis was graded.

Curves to show average severity of untreated osseous syphilis (Figs. 4 through 7) were obtained by smoothing average values within indicated age groups. Though only approximate, these illustrate a definitely changing severity with age. Modifications may be necessary when data are available for a larger number. Average *total* severity (Fig. 4) increases during the first three months, then declines relatively rapidly for three months, and more slowly thereafter. Osteochondritis and osteomyelitis rapidly increase in severity during the first 90 days, the former reaching its peak slightly earlier; they then subside to become relatively insignificant after 6 months of age and negligible after one year. Periostitis, on the other hand, increases in severity more slowly to its peak at about 6 months, then slowly declines.

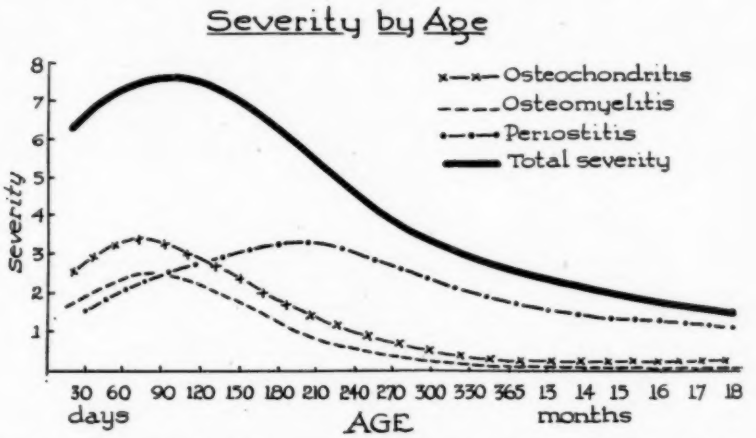


Fig. 4.—Empirically graded average severity of osseous lesions in ninety-eight untreated syphilitic infants (discontinuous observations, see Tables I to IV).

In Fig. 5 is indicated the total severity of untreated osseous syphilis where comparable serial gradings were possible. Reasons for occasional prolonged intervals without treatment need not concern us here. These individuals are contrasted with the curve of average total severity for age (see Fig. 4). It is noteworthy that the curve of average total severity reflects the fluctuations seen in serial observations. Particular attention should be paid to the extremely rapid increases in severity during the first 3 months of life. These fluctuations have been previously reported.[20]

Vogt[21] suggested that the high frequency of normal roentgenograms in syphilitic infants over one year of age may be related to survival of those with milder syphilis, and that the favorable late observations are biased by the higher fatality rate among infants with severe osseous syphilis. Whereas

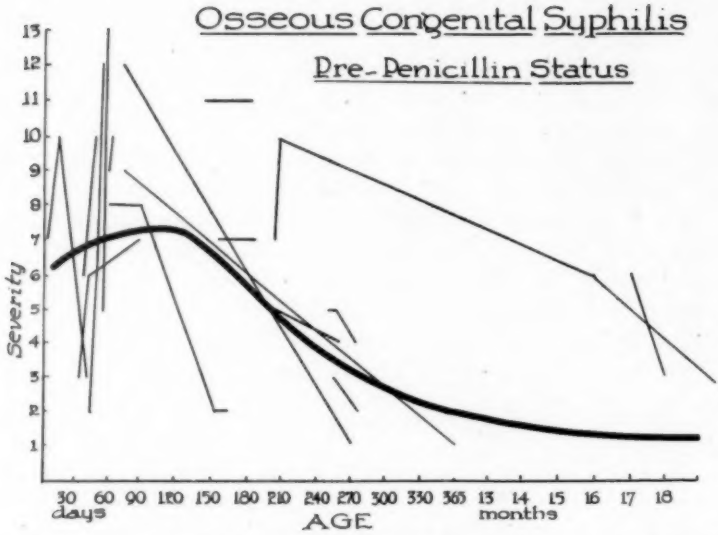

Osseous Congenital Syphilis
Pre-Penicillin Status
Severity
1 2 3 4 5 6 7 8 9 10 11 12 13
30 60 90 120 150 180 210 240 270 300 330 365 13 14 15 16 17 18
days
AGE
months

Fig. 5.—Serial observations for sixteen infants contrasted with smoothed curve of average total severity; all untreated.

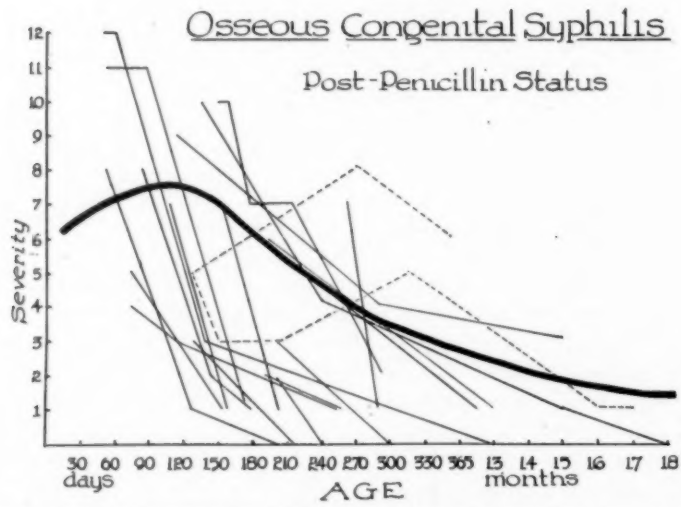

Osseous Congenital Syphilis
Post-Penicillin Status
Severity
1 2 3 4 5 6 7 8 9 10 11 12
30 60 90 120 150 180 210 240 270 300 330 365 13 14 15 16 17 18
days
AGE
months

Fig. 6.—Serial observations for twenty infants following penicillin therapy contrasted with curve of average total severity for those untreated. Dotted lines indicate status of osseous lesions in two infants who relapsed clinically.

infants with clinically severe congenital syphilis often have severe osseous lesions,[20] serial observations (Fig. 5) indicate that even without treatment these heal along a fairly orderly time pattern. For the present, correction of control observations for expected fatality rates is not possible.

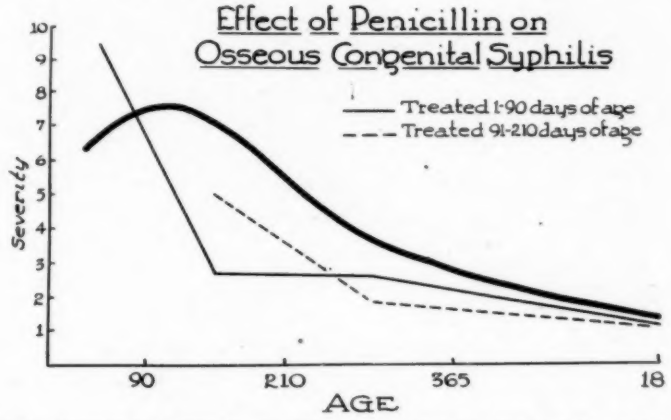


Fig. 7.—Average total severity, treated and untreated (see Tables I, V, and IX).

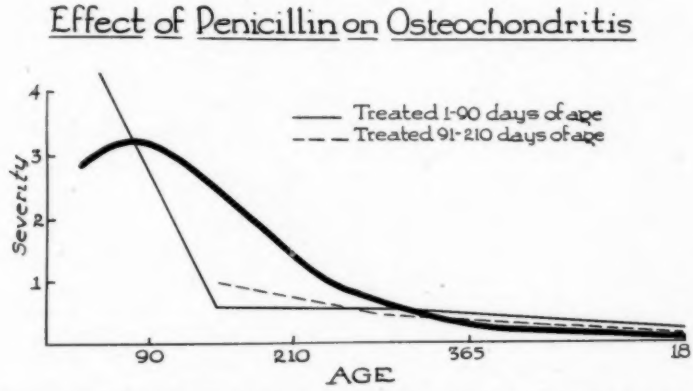


Fig. 8.—Average severity of osteochondritis, treated and untreated (see Tables II, VI, and X).

There have been few reports[10, 21, 22] concerning effects of antisyphilitic therapy upon osseous lesions; comparison between rates of healing of untreated and treated osseous syphilis has not been made. The clinical material, of which this study comprises a part, the dosage schedules employed, and clinical and serologic results of treatment with penicillin have been reported elsewhere.[23, 24, 25] No attempt is made here to correlate rate of healing with particular dosage schedules of penicillin. The small number of patients treated with similar schedules in each age group precludes their comparison.

Serial examinations following treatment (Fig. 6) were contrasted with the average total severity derived for those untreated. These few observations indicate that healing is rapid in infants treated during the first three months of life, but slow in those treated later. Figs. 7, 8, 9, and 10 portray average

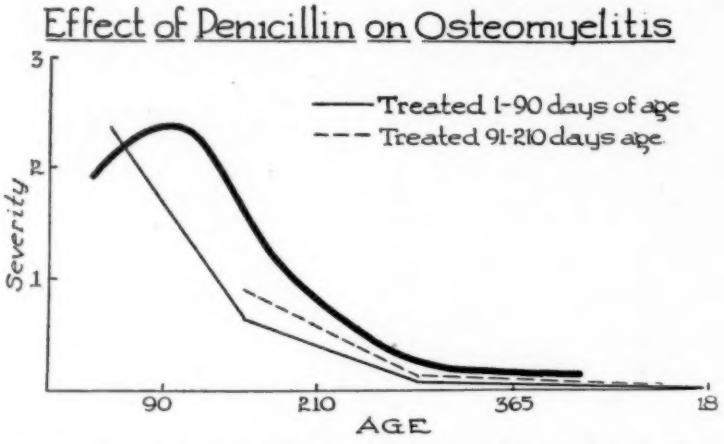


Fig. 9.—Average severity of osteomyelitis, treated and untreated (see Tables III, VII, and XI).

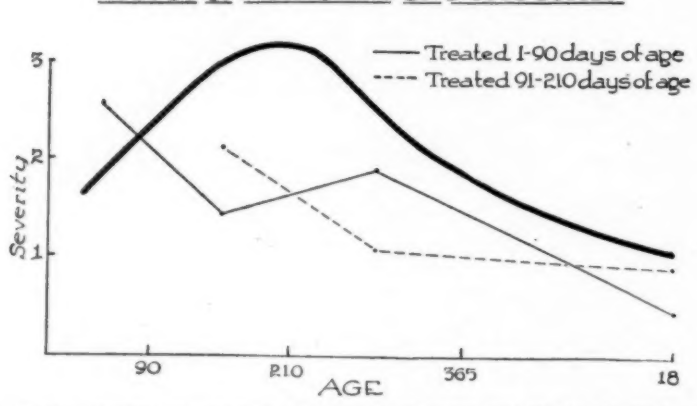


Fig. 10.—Average severity of periostitis, treated and untreated (see Tables IV, VIII, and XII).

severities following treatment with penicillin for two groups, those treated before 90 days of age and those treated during the next four months. Included for comparative purposes are smoothed curves to show average severity of untreated osseous syphilis and its separate manifestations.

Statistical analysis is required to ascertain whether these observed differences in rates of healing are significant. Since age is the major factor, it must

be the basis for comparison. Intervals were selected by inspection of the curve for total severity of untreated lesions: one to 90 days of age represents the period of increasing severity, 91 to 210 days that of rapidly decreasing severity, 211 to 365 days that of moderate decline, and 13 to 24 months that of slow decline. Unfortunately, adequate roentgenographic observations were available only for those infants treated during the first two of these periods (Tables V through XII). Techniques* adapted for analysis of small samples were employed, and the means of corresponding age groups in treated and untreated infants were compared by obtaining the relative deviate (k) between the means. Because the numbers involved are small, only high values of k were considered significant; a value of k greater than 3.5 indicates a probability of less than 5 out of 10,000 that an observed difference between the means would be due to errors in random sampling.

TABLE V. POSTPENICILLIN STATUS OF OSSEOUS CONGENITAL SYPHILIS IN TWENTY-EIGHT INFANTS TREATED AT 1 TO 90 DAYS OF AGE

DISTRIBUTION OF LESIONS BY MANIFESTATION AND AGE				
	AGE			
MANIFESTATIONS	1-90 DAYS	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	11	19	12	4
Number of observations	13	25	13	6
Normal	0	4	3	2
Osteochondritis only	0	0	2	1
Osteomyelitis only	0	0	0	0
Periostitis only	0	10	5	3
Osteochondritis and osteomyelitis	0	0	0	0
Osteochondritis and periostitis	1	4	2	0
Osteomyelitis and periostitis	0	4	0	0
Osteochondritis, osteomyelitis and periostitis	12	3	1	0
SEVERITY				
$\bar{x}$	9.462	2.680	2.462	1.667
$S.D._x$	3.18	2.59	2.65	0.62
M.L.E.	3.31	2.64	2.76	0.68
$S.E._{\bar{x}}$	0.96	0.54	0.80	0.30
k	0.25	5.18	0.48	1.34
Significance	none	high	none	none

*Mean $(\bar{x}) = \frac{\Sigma x}{N}$

Standard Deviation $(S.D._x) = \sqrt{\frac{\Sigma x^2}{N} - \bar{x}^2}$

Maximum likelihood estimate of standard deviation $(M.L.E.) = S.D._x \sqrt{\frac{N}{N-1}}$.

Standard error of the mean $(S.E._{\bar{x}}) = \frac{S.D._x}{\sqrt{N-1}}$.

Relative deviate between the means $(k) = \frac{\bar{x} - \bar{y}}{\sqrt{S.E._{\bar{x}}^2 + S.E._{\bar{y}}^2}}$.

Values of $k > 1.96$ ($P < 0.05$), questionably significant.

Values of $k > 2.80$ ($P < 0.005$), probably significant.

Values of $k > 3.5$ ($P < 0.0005$), highly significant.

TABLE VI. POSTPENICILLIN STATUS OF OSTEOCHONDRITIS IN TWENTY-EIGHT INFANTS TREATED AT 1 TO 90 DAYS OF AGE

RELATION OF TYPE TO AGE				
	AGE			
TYPE	1-90 DAYS	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	11	19	12	4
Number of observations	13	25	13	6
Absent	0	18	8	5
Type I	3	1	3	1
Type II	6	1	0	0
Type III	1	5	0	0
Type IV	3	0	1	0
Type V	3	1	1	0
Type VI	3	0	0	0
Type VII	3	0	0	0
Type VIII	2	0	0	0
SEVERITY				
$\bar{x}$	4.308	0.640	0.615	0.167
$S.D._x$	2.61	1.20	0.92	0.37
M.L.E.	2.72	1.22	0.96	0.41
$S.E._{\bar{x}}$	0.78	0.25	0.28	0.18
k	1.39	3.83	0.77	1.49
Significance	none	high	none	none

TABLE VII. POSTPENICILLIN STATUS OF OSTEOMYELITIS IN TWENTY-EIGHT INFANTS TREATED AT 1 TO 90 DAYS OF AGE

RELATION OF TYPE TO AGE				
	AGE			
TYPE	1-90 DAYS	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	11	19	12	4
Number of observations	13	25	13	6
Absent	1	18	12	6
Type I	6	2	1	0
Type II	3	1	0	0
Type III	5	4	0	0
Type IV	2	1	0	0
SEVERITY				
$\bar{x}$	2.615	0.680	0.154	0.00
$S.D._x$	1.27	0.58	0.54	0.00
M.L.E.	1.32	0.59	0.56	0.00
$S.E._{\bar{x}}$	0.38	0.12	0.16	0.00
k	1.35	3.93	0.02	1.45
Significance	none	high	none	none

This analysis reveals no significant difference in rates of healing for treated and untreated groups unless therapy is given before the age of 3 months. Significant acceleration continuing for about four months after such early treatment is largely due to improvements in osteochondritis and osteomyelitis. A similar difference of only probable significance occurs for periostitis. After seven months, differences in rates of healing are not significant. Therapy administered in the interval between 3 to 7 months caused no significant acceleration.

Serial roentgenograms were obtained in thirty-four infants during or shortly after treatment with penicillin; a temporary increase in severity was observed four times (Table XIII), each within the first 3 months of life. As noted previously, rapid fluctuations of untreated osseous lesions characterize this early age, the period of exacerbation. Inasmuch as there is also a lag in improvement after therapy given at this age, it seems probable that penicillin is not responsible for this phenomenon. Indeed, it is remarkable that exacerbations were not more common among these youngest infants. One possible explanation for these has been given by Levin,[19] who noted a fall in levels for ascorbic acid during intensive arsenical therapy administered in the first 6 months of life. The degree to which this affects healing remains conjectural.

TABLE VIII. POSTPENICILLIN STATUS OF PERIOSTITIS IN TWENTY-EIGHT INFANTS TREATED AT 1 TO 90 DAYS OF AGE

RELATION OF TYPE TO AGE				
	AGE			
TYPE	1-90 DAYS	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	11	19	12	4
Number of observations	13	25	13	6
Absent	0	4	5	3
Type I	13	14	2	0
Type II	7	1	0	0
Type III	2	3	4	1
Type IV	0	9	8	3
Type V	0	0	1	0
SEVERITY				
$\bar{x}$	2.538	1.360	1.769	1.000
S.D.$_x$	1.08	1.20	1.93	1.41
M.L.E.	1.12	1.22	2.01	1.54
S.E.$_{\bar{x}}$	0.32	0.25	0.58	0.69
k	2.55	2.84	0.86	0.67
Significance	questionable	probable	none	none

TABLE IX. POSTPENICILLIN STATUS OF OSSEOUS CONGENITAL SYPHILIS IN TWENTY-TWO INFANTS TREATED AT 91 TO 210 DAYS OF AGE

DISTRIBUTION OF LESIONS BY MANIFESTATION AND AGE			
	AGE		
MANIFESTATIONS	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	10	14	7
Number of observations	14	17	8
Normal	0	5	2
Osteochondritis only	0	3	0
Osteomyelitis only	0	0	0
Periostitis only	7	6	5
Osteochondritis and osteomyelitis	0	0	0
Osteochondritis and periostitis	2	1	1
Osteomyelitis and periostitis	0	1	0
Osteochondritis, osteomyelitis, and periostitis	5	1	0
SEVERITY			
$\bar{x}$	4.929	1.882	1.000
S.D.$_x$	3.37	2.30	0.39
M.L.E.	3.50	2.37	0.42
S.E.$_{\bar{x}}$	0.97	0.59	0.16
k	1.47	1.41	2.60
Significance	none	none	questionable

TABLE X. POSTPENICILLIN STATUS OF OSTEOCHONDRITIS IN TWENTY-TWO INFANTS TREATED AT 91 TO 210 DAYS OF AGE

RELATION OF TYPE TO AGE			
	AGE		
TYPE	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	10	14	7
Number of observations	14	17	8
Absent	7	12	7
Type I	0	2	1
Type II	3	0	0
Type III	1	1	0
Type IV	3	1	0
Type V	0	1	0
Type VI	0	0	0
Type VII	0	0	0
Type VIII	0	0	0
SEVERITY			
$\bar{x}$	1.000	0.529	0.125
$S.D._x$	1.0	0.92	0.33
M.L.E.	1.04	0.95	0.35
$S.E._{\bar{x}}$	0.29	0.24	0.13
k	2.78	0.56	1.71
Significance	questionable	none	none

TABLE XI. POSTPENICILLIN STATUS OF OSTEOMYELITIS IN TWENTY-TWO INFANTS TREATED AT 91 TO 210 DAYS OF AGE

RELATION OF TYPE TO AGE			
	AGE		
TYPE	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	10	14	7
Number of observations	14	17	8
Absent	9	15	8
Type I	0	0	0
Type II	4	2	0
Type III	5	0	0
Type IV	2	0	0
SEVERITY			
$\bar{x}$	1.714	0.235	0.00
$S.D._x$	0.26	0.64	0.00
M.L.E.	0.27	0.66	0.00
$S.E._{\bar{x}}$	0.07	0.16	0.00
k	0.95	0.39	1.45
Significance	none	none	none

Pseudoparalysis, present at the initiation of treatment in fifteen infants, was known to have disappeared within three weeks in twelve; all had cleared within one month. In satisfactory roentgenograms of affected extremities for twelve, osteochondritis and periostitis were invariably present, osteomyelitis was noted eight times, no specific type (Figs. 1, 2, and 3) was common to all, there were no fractures, and empirically graded severity ranged from 4 to 16. Films of eight of these infants were compared with others taken at the time pseudoparalysis disappeared; severity had increased in three, decreased in four, and remained unchanged in one.

The validity of our observations depends on the following assumptions: (1) discontinuous estimates of severity in untreated osseous syphilis constitute adequate control material; (2) grossly inadequate treatment of the pregnant woman does not significantly alter the character of infantile osseous syphilis; (3) differences in osseous syphilis due to various dosages of penicillin employed in our study are unimportant. Testing of these assumptions must await opportunity to study a much larger number of patients.

TABLE XII. POSTPENICILLIN STATUS OF PERIOSTITIS IN TWENTY-TWO INFANTS TREATED AT 91 TO 210 DAYS OF AGE

RELATION OF TYPE TO AGE			
	AGE		
TYPE	91-210 DAYS	211-365 DAYS	13-24 MONTHS
Number of children	10	14	7
Number of observations	14	17	8
Absent	0	8	2
Type I	8	1	0
Type II	0	1	0
Type III	6	3	0
Type IV	5	7	6
Type V	0	0	1
SEVERITY			
$\bar{x}$	2.214	1.118	0.875
S.D.$_{\bar{x}}$	1.21	1.41	0.60
M.L.E.	1.26	1.45	0.64
S.E.$_{\bar{x}}$	0.35	0.36	0.24
k	0.27	2.44	1.45
Significance	none	questionable	none

TABLE XIII. STATUS OF OSSEOUS SYPHILIS IMMEDIATELY FOLLOWING PENICILLIN THERAPY*

AGE AT START OF PENICILLIN	INTERVAL AFTER START OF PENICILLIN (DAYS)	STATUS OF OSSEOUS LESIONS AT INDICATED INTERVAL			NO. INFANTS
		WORSE	NOTE CHANGE	IMPROVED	
1-90 days	1–15	3	4	2	9
	16–30	–	1	1	2
	31–45	1	1	2	4
	46–60	–	1	3	4
		4	7	8	19
91-210 days	1–15		3	–	3
	16–30		1	3	4
	46–60		–	3	3
			4	6	10
211-365 days	41–60		–	2	2
13-24 months	31–45		–	1	1
	46–60		1	1	2
			1	2	3

*The number of days between the last prepenicillin roentgenogram and start of penicillin therapy was less than four in sixteen infants, less than eight in ten, less than eleven in three, and less than fifteen in five.

CONCLUSIONS

1. The behavior of osseous congenital syphilis in untreated infants follows a fairly definite pattern of rapidly increasing severity during the first 3 months

of life and slow healing thereafter. Improvement results from decreasing severity of osteomyelitis and osteochondritis; periosteal changes increase in prominence over a longer period and persist as the commonest residua. The course of a given lesion in any individual patient cannot be accurately predicted.

2. Dosages of penicillin employed so far have temporarily accelerated healing of osseous syphilis only in infants treated during the first three months of life. This acceleration, as in untreated controls, occurs principally in osteochondritis and osteomyelitis; simultaneous improvement in periostitis is only of probable significance. No such significant effects were observed among those treated during the next four months. The mode of healing for any particular type of lesion, as herein described, has not been evaluated.

3. Increase in severity of these lesions during or shortly after penicillin therapy occurs in an age group where this phenomenon is to be expected without treatment.

4. Pseudoparalysis disappears without any specific changes in the roentgenograms; indeed, osseous lesions may even appear worse after pseudoparalysis subsides.

ADDENDUM

To determine whether arbitrary changes in weighted severity would alter these conclusions, data were reanalyzed as follows: The weight of types III and IV was increased to 3, that of types V and VI to 10, and of types VII and VIII to 5. Osteomyelitis of type III was increased to 10, and of type IV reduced to 2. Periostitis, type III, was also reduced to 2. An increased value was thus placed on lesions commonly considered to be more specific for syphilis. If penicillin affects osseous syphilis, this maneuver should accentuate any difference between treated and untreated groups; but actually the observed discrepancy was only slight. A highly significant difference appeared only in the total severity of the group treated in the first three months of life and observed at 91 to 210 days of age. No other differences were of more than probable significance. In the group treated during the first three months of life, the latter differences appeared in osteochondritis observed at 91 to 210 days of age and in periostitis observed at one to 90 and 91 to 210 days of age. In infants treated from the third to seventh month of life a difference of only probable significance also occurred in osteochondritis observed at 91 to 210 days. Under the conditions of this study it would seem doubtful, therefore, that penicillin effected more than a transitory increase in the rate of healing of osseous syphilis in those infants treated under 90 days.

REFERENCES

1. Ingraham, N. R., Jr.: The Lag Phase in Early Congenital Osseous Syphilis Roentgenographic Study, Am. J. M. Sc. **191**: 819, 1936.
2. Black, W. C.: Diagnosis of Congenital Syphilis; Pathognomonic Criteria, J. PEDIAT. **14**: 761, 1939.
3. Ingraham, N. R., Jr., Stokes, J. H., Beerman, H., Lantz, J. W., and Wammock, V. S.: Penicillin Treatment of the Syphilitic Pregnant Woman, J. A. M. A. **130**: 683, 1946.
4. Goodwin, M. S., and Moore, J. E.: Penicillin in Prevention of Prenatal Syphilis, J. A. M. A. **130**: 688, 1946.
5. Christie, A.: The Value of Roentgenographic Examination in the Diagnosis of Syphilis in Newborn Infants, J. PEDIAT. **15**: 230, 1939.
6. McKelvey, J. L., and Turner, T. B.: Syphilis and Pregnancy; Analysis of the Outcome of Pregnancy in Relation to Treatment in 943 Cases, J. A. M. A. **102**: 503, 1934.
7. Podlasky, H. B., and Enzer, N.: The Comparative Value of Serologic and Roentgenologic Diagnoses of Congenital Syphilis, Radiology **20**: 337, 1933.

8. Eliot, M. M., Souther, S. P., and Park, E. A.: Transverse Lines in X-Ray Plates of the Long Bones of Children, Bull. Johns Hopkins Hosp. **41**: 364, 1927.
9. Ingraham, N. R., Jr., Shaffer, B., Spence, B. E., and Gordon, J. H.: The Adequate Diagnosis of Infantile Congenital Syphilis, Arch. Dermat. & Syph. **43**: 323, 1941.
10. Pendergrass, E. P., and Bromer, R. S.: Congenital Bone Syphilis; Preliminary Report; Roentgenologic Study With Notes on the Histology and Pathology of the Condition, Am. J. Roentgenol. **22**: 1, 1929.
11. Caffey, J.: Syphilis of Skeleton in Early Infancy; the Non-specificity of Many of the Roentgenographic Changes, Am. J. Roentgenol. **42**: 637, 1939.
12. McLean, S.: II. Correlation of Roentgenographic and Pathologic Aspects of Congenital Osseous Syphilis, Am. J. Dis. Child. **41**: 363, 1931.
13. McLean, S.: V. Osseous Lesions of Congenital Syphilis; Summary and Conclusions in 102 Cases, Am. J. Dis. Child. **41**: 1411, 1931.
14. Caffey, J., and Silverman, W. A.: Infantile Cortical Hyperostoses: Preliminary Report on New Syndrome, Am. J. Roentgenol. **54**: 1, 1945.
15. Smythe, F. S., Potter, A., and Silverman, W.: Periosteal Reaction, Fever, and Irritability in Young Infants, Am. J. Dis. Child. **71**: 333, 1946.
16. Park, E. A., and Jackson, D. A.: Irregular Extensions of the End of Shaft in the X-ray Photograph in Congenital Syphilis, With Pertinent Observations, J. PEDIAT. **13**: 748, 1938.
17. Roberts, M. H.: Congenital Syphilis, Am. J. Dis. Child. **45**: 461, 1933.
18. Russo, P. E., and Shryock, L. F.: Bone Lesions of Congenital Syphilis in Infants and Adolescents; Report of 46 Cases, Radiology **44**: 477, 1945.
19. Levin, I. M.: Scurvy, Am. J. Dis. Child. **66**: 97, 1943.
20. McLean, S.: IV. Correlation of Clinical Picture With Osseous Lesions of Congenital Syphilis as Shown by the X-rays, Am. J. Dis. Child. **41**: 887, and 1128, 1931.
21. Vogt, E. C.: Value of Roentgenography in Diagnosis of Congenital Syphilis; Infants Considered, Am. J. Roentgenol. **26**: 96, 1931.
22. Sutherland, G. F., and Mitchell, J. H.: Effects of Treatment on Bone Lesions in Congenital Syphilis, J. A. M. A. **81**: 1752, 1923.
23. Platou, R. V., Hill, A. J., Jr., Ingraham, N. R., Jr., Goodwin, M. S., Wilkinson, E. E., and Hansen, A. E.: Penicillin in Treatment of Infantile Syphilis; a Brief Preliminary Report, J. A. M. A. **127**: 582, 1945.
24. Platou, R. V., Hill, A. J., Jr., Ingraham, N. R., Jr., Goodwin, M. S., Wilkinson, E. E. and Hansen, A. E.: Effect of Penicillin in the Treatment of Infantile Congenital Syphilis, Further Observations, Am. J. Dis. Child. **72**: 635, 1946.
25. Platou, R. V., Hill, A. J., Jr., Ingraham, N. R., Jr., Goodwin, M. S., Wilkinson, E. E., Hansen, A. E., and Heyman, A.; Early Congenital Syphilis; Treatment of 252 Patients With Penicillin, J. A. M A. **133**: 10, 1947.

CELIAC SYNDROME

VI. The Relationship of Celiac Disease, Starch Intolerance, and Steatorrhea

Dorothy H. Andersen, M.D.
New York, N. Y.

FOR some years my co-workers and I have been studying chronic malnutrition and chronic indigestion in infants and children, with especial reference to those patients presenting the celiac syndrome. One object of this project has been to find means of separating these cases into groups on the basis of etiology and pathogenesis, with the hope that informed therapy might be more consistently effective than the trial-and-error methods which have been necessary in the past. In somewhat less than one-half of the cases a satisfactory morphologic or bacteriologic explanation has been found, for example: fibrocystic disease of the pancreas, stenosis of the ileum, or chronic enteric infection due to Ascaris, Giardia or Salmonella. The cases in which no anatomic or bacteriologic basis for the disease has been found, however, form the major portion of our series. This is a preliminary report on the observations on the latter "idiopathic" group, which is referred to as the group of patients with celiac disease. This report represents a summary of the present status of the investigation, and an incomplete report of the data on which our concept of celiac disease is based. The remaining evidence on the technical details will be reported later.

The term celiac disease, as used in this paper, is applied to those patients who have chronic or recurrent diarrhea some time between the sixth month and sixth year, without demonstrable bacteriologic or anatomic basis, and who are intolerant of a normal diet for their age, respond to dietary therapy, and at some time in their course have a protuberant abdomen and a slow gain in weight. For reasons to be given later, the presence of steatorrhea has not been required for the diagnosis of celiac disease. The data to be presented were obtained from eighty-three patients who fulfilled these criteria and in whom both assay of pancreatic enzymes in the duodenal juice and chemical analysis of feces for fat were done. Cases of fibrocystic disease of the pancreas were excluded on the basis of failure to demonstrate normal levels of trypsin in the duodenal juice, a criterion which previous experience has shown to be reliable. The cases differed in severity, but all were sufficiently severe for hospitalization.

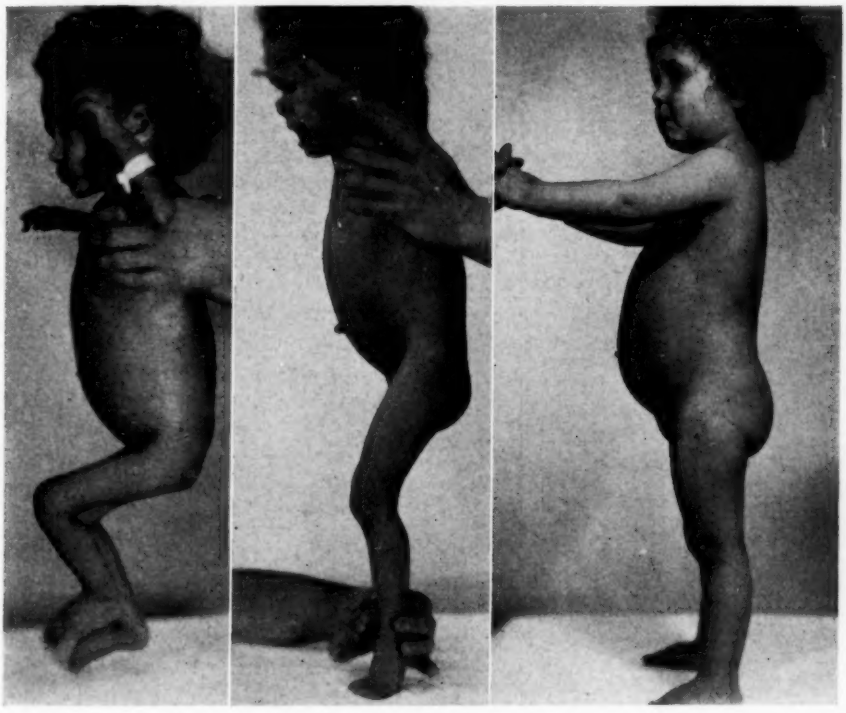
First to be considered is the course of the disease in the more severe cases, with an illustrative example.

R. T., a girl, was admitted to Babies Hospital at the age of 22 months in a severe state of malnutrition and with a weight of 12 pounds. At birth she had appeared normal and vigorous. Beginning in the neonatal period, however, there were bouts of diarrhea lasting

From the Departments of Pediatrics and Pathology, College of Physicians and Surgeons, Columbia University and Babies Hospital.

Presented before the Fifteenth Annual Meeting of the American Academy of Pediatrics, Pittsburgh, Pa., Feb. 24-27, 1947.

from four to six weeks and recurring every two or three months. These episodes began with a respiratory infection and fever, promptly followed by watery diarrhea with from ten to fifteen stools a day. After a week or more the diarrhea gradually decreased in severity, the stools became large, pale, and pasty, and after a month or so numbered one to two daily. After a respite of a month or more, the cycle repeated itself. At about 12 months of age the abdomen was observed to be large. Her appetite had been poor and gain was slow, with a peak weight of 14 pounds at 14 months. Her development was delayed:



A. *B.* *C.*

Fig. 1.—R. T. *A*, On admission, at 22 months of age. *B*, At 24 months of age. *C*, At 3 years.

she sat alone at 14 months. Her first teeth appeared at 18 months and she had never stood alone. A variety of diets had proved unsuccessful. For the eight months prior to her admission she had been in another hospital where she had received parenteral fluids during the acute episodes and parenteral therapy with vitamin B complex and liver concentrates without benefit. Her diet had consisted of a formula of evaporated milk, rice flour and water, and cereals. Because of her failure to respond to parenteral vitamin therapy, the diagnosis of celiac disease was questioned. However, the response to a modified diet in association with vitamin therapy was prompt and continued (Figs. 1 and 2). The two dips in her later weight curve correspond to brief periods of large foul stools following respiratory infections. Her progress has been otherwise uneventful. She is still on a modified diet.

The course of this patient consists of three periods: (1) a prodromal period during which there were bouts of diarrhea associated with upper respiratory

infections, with the first episode occurring during the first month of life; (2) a critical period starting at about one year of age, with loss of weight and the physical appearance associated with celiac disease; this continued for about one year until the institution of appropriate dietary therapy; and (3) a prolonged maintenance period during which the child was well while she remained on a modified diet but had several relapses when the regime was made more liberal.

Analysis of our series of eighty-three cases shows that the symptoms of indigestion, usually with diarrhea predominating, began before the age of 6 months in about one-third of the cases, between 6 and 12 months in another third, and between one and 3 years in the remainder. The diet and supplements prior to the onset of diarrhea were adequate in nearly every case, and the onset of the disease was insidious. The manner of onset varied. In some instances the stools were observed to be usually large but not watery prior to the first bout of diarrhea; sometimes the child had several bouts of diarrhea and then refused feedings, ceased to have diarrhea, and lost weight. In the majority of cases the episodes of diarrhea began with an upper respiratory infection, often a mild one.

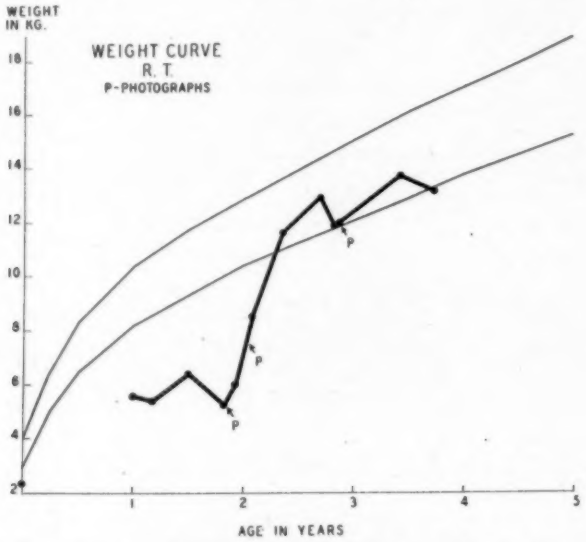


Fig. 2.—Weight curve for R. T. showing response to therapy and the times at which the photographs of Fig. 1 were taken.

The critical period sometimes followed a rapid succession of such respiratory infections associated with diarrhea, and not infrequently it has followed the introduction of a restricted bland diet designed to control the diarrhea. In several cases the diarrhea has become uncontrollable after some weeks or months of an elimination diet given in the belief that the symptoms were due to food allergy. Occasionally the classical picture of severe celiac disease develops without apparent precipitating factors. Usually, however, the precipitating factors are

of a kind which might be expected to lead to nutritional deficiency. Most of the symptoms of the critical period disappear with remarkable and gratifying rapidity with appropriate dietary and vitamin therapy. The evidence is strong that the critical period represents a multiple deficiency state which is almost always reversible, with the present knowledge of vitamins. In the present series

Fig. 3.—R. F., aged 11 months.

there has been one fatality among the thirty-seven cases which showed the classical symptoms in severe degree. We may learn of the course of the patients who have been inadequately treated from the reports that antedate the knowledge of vitamins such as the classical ones of Gee,[1] Herter,[2] and Fanconi.[3] In 1939 Hardwick[4] summarized the data on mortality. From his figures an average mortality of 15 per cent is calculated, the majority of the deaths occurring in the second and third years. Many of the survivors ran a chronic course and were ultimately dwarfed and sometimes deformed (Parsons[5]). The low mortality and excellent recovery of the present series is in contrast.

The maintenance phase of the disease is prolonged. For the first year or so after the normal weight is recovered the patients may continue to have brief recurrences of diarrhea precipitated either by a respiratory infection or by a

break in diet. After an interval of one to several years it is possible to relax the dietary restrictions somewhat without ill effect, and by school age these restrictions can usually be mild. My personal experience does not as yet go further. Late recurrences, even in adult life, have been observed, and these may respond less readily to treatment.

The general pattern of the disease in different patients shows an almost monotonous uniformity, with some variation in the age at which the critical period manifests itself. The weight curves and serial photographs of several patients are shown to emphasize this point. It is of interest that the patients with crisis before the first year do not show as striking a change in body contours as do those who have experienced a longer prodromal period and an onset of the critical period after the age of 18 months. (Compare Figs. 3, 5, and 7.)

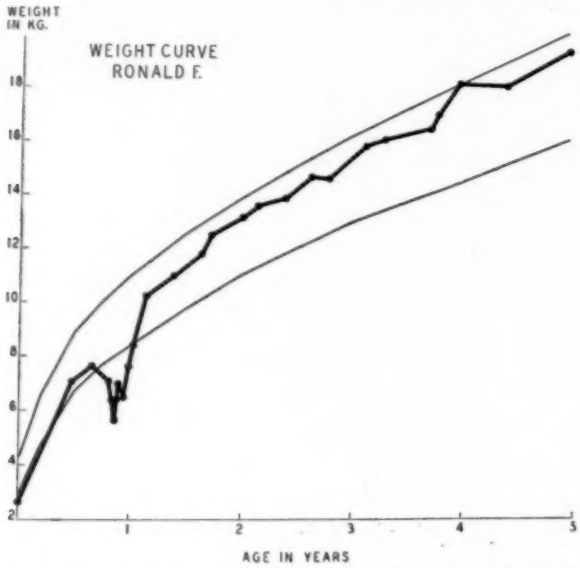
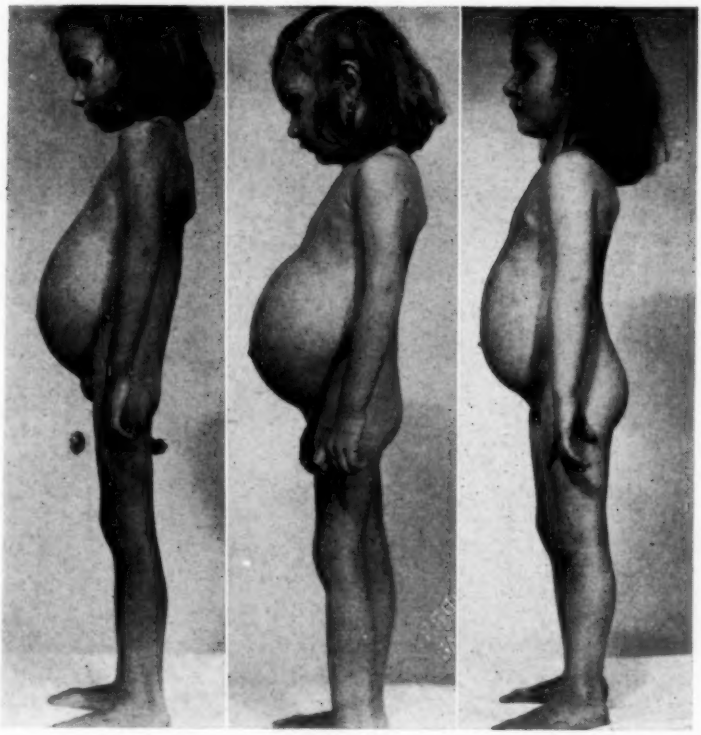


Fig. 4.—Weight curve of R. F., given as an example of the course of patients with the critical period during the first year of life.

It would appear, from the course of the disease, that the critical period constitutes a multiple deficiency syndrome superimposed upon a constitutional defect, and bears to this defect a relationship comparable to that which diabetic coma bears to diabetes. If this be true, as I believe it is, it becomes important to distinguish the clinical and laboratory findings which are the result of nutritional deficiency from those which are a part of the basic process. The two criteria available to us are: (1) the recognition of changes known to be due to the deficiency of a specific substance, for example, scurvy, rickets, keratomalacia, cheilosis, hypoprothrombinemia, and macrocytic anemia, any of which may be encountered occasionally in celiac disease; (2) demonstration that phenomena

as yet not known to be the result of the lack of a specific substance are transitory and respond to a diet containing foods known to be good sources of a variety of nutritional substances. The residual phenomena which are consistently found both early in the course of the disease and also after the child has regained normal weight and activity may tentatively be considered as part of the basic process.



A. *B.* *C.*

Fig. 5.—B. H. *A*, At 3½ years. *B*, Six weeks later. *C*, At 3 years, 11 months. During the early stages of improvement, the abdomen becomes larger; later, the abdominal enlargement becomes moderate and there is a tendency to obesity.

There is evidence that several phenomena consistently found during the critical period but not known to be due to the deficiency of a specific substance are transitory and hence are probably not essential parts of the basic process. Among these is steatorrhea, which will be discussed more fully, since it has been long considered essential to the diagnosis of celiac disease. In obtaining the data to be presented, a standard procedure was followed. These data consist of a series of analyses of the feces for fat, and in all instances the feces were collected while the patient was receiving a normal diet for his age, which included whole milk, either pasteurized or evaporated. The patient was placed on the diet twenty-four to forty-eight hours before the beginning of the stool collection, and

this diet was continued throughout the three-day period of the collection. The total material was placed in a single container, thoroughly mixed, and aliquots were then taken for various analyses. The results are reported in terms of per cent of dried weight as total fat and also as the mean weight of fat excreted per day.

The evidence that steatorrhea is not part of the basic process may be summarized as follows:

The first observation was that some patients who present the complete physical appearance of celiac disease and who excrete large, pale, foul stools do not in fact have an excess of fat in the feces either before or after the appearance of diarrhea on a normal diet (Table I). It was this observation that led me, some years ago, to postulate the existence of starch intolerance as a disease entity distinct from celiac disease, an hypothesis which subsequent experience has led me to retract.

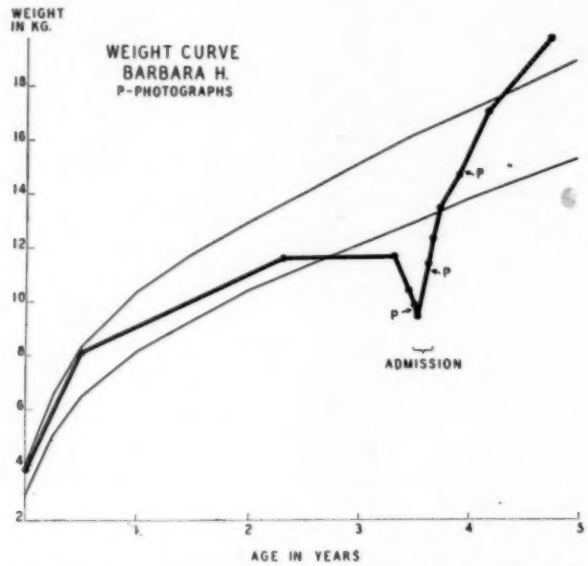


Fig. 6.—B. H. Weight curve showing long prodromal period preceding the critical period at 3 years.

Patients who showed marked steatorrhea on the first examination made after admission to the hospital usually no longer showed steatorrhea after clinical improvement, the change taking place within a period of less than a year (Table II).

Patients who, on admission, were considered so ill that trial with normal diet was hazardous but who were placed on a normal diet after a few weeks of therapy were sometimes found to have no excess of fecal fat. In nine patients a preliminary microscopic examination of the feces showed an excess of fat even though the patient was receiving a limited fat intake and a protein milk formula,

but examination a few weeks later while the patient was on a normal diet including whole milk revealed no excess of fat by either microscopic or chemical examination. I present the photographs and weight curve of one such patient (Figs. 9 and 10) to demonstrate the severity of the disease and the similarity to the cases with steatorrhea previously presented.

The time required for the disappearance of steatorrhea after the initiation of therapy has not been determined with exactness, chiefly because the possibility that it might be brief did not occur for some time. An estimate may be made by arranging the data obtained from the more severely ill patients with respect to the interval between admission to the hospital and the determination of the relative amount of fat in the feces (Table III). From these data it would appear that steatorrhea is usually overcome within one month of the beginning of therapy, and in the present series it has been found after two months in only one case. It is not uncommon, however, to find a mild increase in fecal fat in terms of grams of fat excreted per day when the total daily

TABLE I. FECAL FAT IN CELIAC DISEASES BEFORE AND AFTER "BREAK" ON NORMAL DIET IN PATIENTS WITHOUT STEATORRHEA

	BEFORE					AFTER			
PATIENT	AGE (MO.)	STOOL (GM./DAY WET WT.)	WATER (%)	FAT (% DRY WT.)	FAT (GM./ DAY)	STOOL (GM./DAY WET WT.)	WATER (%)	FAT (% DRY WT.)	FAT (GM./ DAY)
C. C.	14	–	84.1	15	–	75	84.4	14	2.1
M. S.	17	38	71.2	12	1.3	–	73.7	7	–
M. M.	21	49	70.4	27	3.9	88	81.4	25	4.0
J. F.	26	32	74.7	9	0.8	40	79.0	12	1.0
Controls (Mean and S.D.)	12 to 24	34.6 ±14.7	77.5 ±4.0	13.7 ±5.6	0.95 ±0.33				

TABLE II. STOOL FAT AND CELIAC DISEASE; EFFECT OF TREATMENT ON STEATORRHEA

	BEFORE				AFTER			
PATIENT	AGE	STOOL (GM./DAY WET WT.)	FAT (% DRY WT.)	FAT (GM./ DAY)	AGE	STOOL (GM./DAY WET WT.)	FAT (% DRY WT.)	FAT (GM./ DAY)
E. J.	7 months	69	43	6.7	8 months	56	17	2.0
R. F.	11 months	43	48	5.3	21 months	44	12	1.0
S. E.	16 months	80	34	3.8	24 months	61	11	1.1
R. T.	22 months	25	57	1.7	2¾ years	76	21	3.7
L. I.	3½ years	62	44	6.0	4 years	93	26	2.6
M. G.	4 years	150	24	7.9	4⅙ years	128	17	2.8
Controls	6 to 12 months	26 ±10.5	18 ±4.9	1.0 ±0.4				
(Mean and S.D.)	1 to 2 years	35 ±14.7	14 ±5.6	1.0 ±0.3				
	2 to 6 years	26 ±15.5	15 ±2.7	1.0 ±0.5				

TABLE III. RELATION BETWEEN DURATION OF THERAPY AND EXCESS FECAL FAT IN PATIENTS WITH THE CLASSICAL CLINICAL PICTURE OF SEVERE CELIAC DISEASE: NUMBER OF CASES

FECAL FAT (% DRIED WT.)	DURATION OF THERAPY IN WEEKS								
	1	2	3	4	5	6	7	8	>8
Over 30%	10	2	2	4	0	0	1	0	1
Under 30%	5	5	3	0	1	3	0	0	12

excretion of feces is excessive. In these circumstances, there is no selective excess in fat excretion, and the absolute increase may be interpreted as the result of mechanical difficulty or of the increase in fecal fat derived from bacteria. The daily excretion rarely exceeds 3 Gm. of fat per day.

Observations on the lipase concentration in the duodenal juice confirm previous reports that this is normal, and that the difficulty in fat utilization cannot be satisfactorily attributed to failure to split fat (Table IV). By elimination, this leads to the assumption that the difficulty must lie either in a later process necessary for absorption of fat, such as the phosphorylation of fatty acids, or in the absorptive process itself, both of which may be assumed to be enzymatic in nature.

TABLE IV. LIPASE IN THE DUODENAL JUICE OF PATIENTS WITH CELIAC DISEASE AND STEATORRHEA

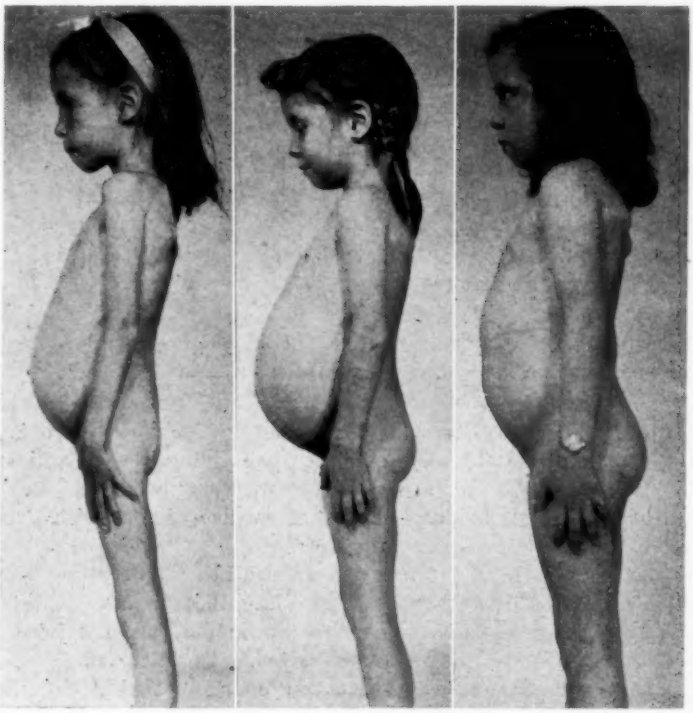
AGE	CONDITION	NO.	LIPASE, UNITS 100/C.C.	
			MEAN	S.D.
6-12 months	Steatorrhea	3	26.1	9.6
	Controls	11	26.1	21.2
1-2 years	Steatorrhea	11	25.1	17.8
	Controls	9	18.8	11.1
2-5 years	Steatorrhea	4	40.7	16.7
	Controls	13	19.6	12.8

The observations just presented provide indirect confirmation of May's earlier one[6] that intensive therapy with vitamin B complex and liver concentrates restores the normal vitamin A absorption curve within a short period, since steatorrhea can be correlated with poor absorption of vitamin A. We are led to the thought that both steatorrhea and poor absorption of vitamin A may be the result of a deficiency of some dietary factor required by the intestine for the normal absorption of fat. The work of May, McCreary, and Blackfan[6] indicates that this substance is to be sought among the members of the vitamin B complex, and the question should be explored further. The records of the patients of the present series provide evidence that therapy with vitamin B complex does not restore complete tolerance to a normal diet nor does it terminate all of the phenomena of the critical period.

It is not possible to discuss here the other phenomena of the critical period, which, in most cases, respond promptly to therapy. Some of them are enumerated as follows: muscle atrophy and consequent flat buttocks; relaxation of ligaments; irritability and apathy; anorexia; a flat glucose tolerance curve; osteoporosis; low concentrations in the serum of cholesterol, lipids, carotene, and positive inorganic ions. These cannot be considered as necessary attributes of the underlying constitutional difficulty.

If the critical period is the expression of a multiple deficiency state which develops under adverse circumstances in patients who have an underlying constitutional defect, it is reasonable to believe that some children with the same basic defect escape the complete expression of the disease. This concept receives

support from the common experience that the clinical picture varies greatly in degree in different cases. Confirmatory evidence is the observation that the incidence of the complete and easily recognized phase of the disease has increased many fold during the war in various cities in Europe, including some where food was relatively abundant though limited in variety, such as London, Copenhagen, and Stockholm. The chief difficulty in establishing the hypothesis that celiac disease is based on an underlying constitutional defect is the dearth of objective criteria of this defect. To return to the analogy with diabetes, it is as though we were unable to make the diagnosis of diabetes in the absence of coma.



A. *B.* *C.*

Fig. 7.—P. M. *A*, At 6 years, 10 months. *B*, Twenty-three days later. *C*, At 7 years, 5 months. The changes are similar to those in the previous cases, although the critical period has occurred at a later age. Improvement in morale is expressed in the hair-do.

The expressions of the basic constitutional disease may be assumed to be present in patients during the critical phase and to persist after the transitory phenomena have responded to dietary therapy. They should also be demonstrable in milder cases in which the complete deficiency state has not been reached. One or more characteristics of the basic disease should be of such nature as to induce diarrhea and a multiple deficiency state. In the course of

these studies, a group of clinical and laboratory findings relating to inadequate digestion of starch has been consistently found in severely ill patients, in those who are convalescent from the critical state, and also in milder cases which have been previously described under the name of starch intolerance. If the presence of steatorrhea is not required for the diagnosis of celiac disease, there are no features which distinguish the patients with starch intolerance from those in the prodromal or recovery phases of celiac disease with steatorrhea. In addition to the factors relating to starch digestion, there are several other phenomena which are so commonly present as to deserve further investigation as to their place in the disease. The characteristics which are consistently present include the following:

1. Pancreatic amylase is absent from the duodenal juice or present in small quantity only. There is clinical intolerance to starch in the diet, clinical response to elimination of starch from the diet, and an excess of starch in the feces when starch is fed.

2. The requirement of dietary protein is greater than normal, as indicated by clinical response to elevated dietary protein and the frequent occurrence of hypoproteinemia in patients who have received dietary protein at levels usually found adequate.

3. There are intermittent attacks of diarrhea, usually beginning in the first year and most severe during the second year, with gradual decrease in severity and frequency as school age is approached.

4. The attacks of diarrhea are usually initiated by an upper respiratory infection and may be controlled either by restriction of the diet or by the administration of sulfadiazine.

5. If the milder cases without steatorrhea be included, there is a high familial incidence of the disease. Commonly, one sibling has celiac disease with steatorrhea and the other is less severely ill with starch intolerance. Several examples of a familial incidence of severe cardiac disease with steatorrhea have been encountered in the past two years.

At the present time the objective findings which are of most value in the recognition of uncomplicated celiac disease are those relating to starch indigestion, specifically the deficiency of amylase in the duodenal juice and the excess of starch in the feces when starch is fed. The importance of these two determinations warrants a brief discussion of the technical difficulties encountered in obtaining and interpreting the data. In regard to the assay of amylase in the duodenal juice, three such obstacles should be considered. The first of these is the frequent admixture of gastric juice with the duodenal contents, resulting in varying degrees of dilution of the pancreatic juice. The use of a double-lumen Einhorn tube with separate openings for the drainage of gastric and duodenal juice has so far not been successfully applied to small infants. In the material obtained with a single tube from the duodenum it may be assumed that the various pancreatic enzymes are equally diluted. Since the method for determining trypsin is more reliable than that for lipase, and since trypsin has been found in high concentration in nearly all cases except

those with fibrocystic disease of the pancreas and those in extreme marasmus, this value has been taken as the figure of reference, and the ratio of amylase to the concentration of trypsin expressed in viscosimetric units has been used in evaluating the degree of amylase deficiency. Comparison of the absolute concentration of amylase in the duodenal juice of patients with celiac disease and controls of like age shows a difference which is statistically significant but less impressive than the difference in the ratio.

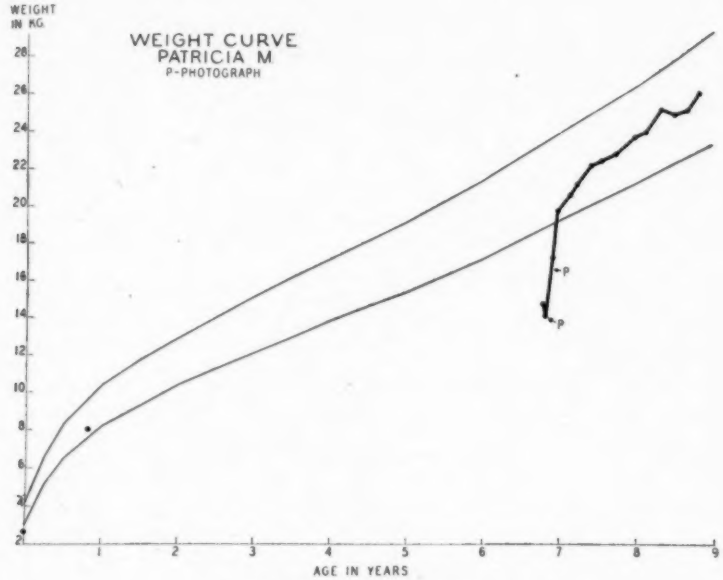


Fig. 8.—P. M. Weight curve.

The second difficulty to be considered is the frequent occurrence of gastric hypoacidity in patients with celiac disease either with or without steatorrhea. When the gastric juice contains little or no free acid it frequently contains amylase which has its source in swallowed saliva. When an admixture of this gastric juice with pancreatic juice is recovered from the duodenum, there may still be some salivary amylase in it, giving an erroneous impression that amylase is being secreted by the pancreas. Thus diluted, the concentration is never high, usually giving a ratio of amylase to trypsin of less than 20 per cent. It is possible to obtain results of this order in the complete absence of pancreatic amylase.

The third technical difficulty results from the fact that amylase is normally absent from the duodenal juice in the neonatal period, and that the normal ratio of amylase to trypsin in the second half of the first year is of the order of 50 per cent, while after one year of age it ranges between 50 per cent and 150 per cent. The determination of amylase concentration cannot therefore be used to sub-

stantiate the diagnosis in infants under 6 months, even though clinical symptoms may appear before this age. As a working rule the value of this ratio which marks the dividing line between normal and abnormal is taken as 20 per cent for patients between 6 and 12 months of age and 40 per cent for those who are older (Table V).

TABLE V. RATIO OF AMYLASE TO TRYPSIN IN THE DUODENAL JUICE IN CELIAC DISEASE EXPRESSED IN VISCOSIMETRIC UNITS

AMYLASE/ TRYPSIN ×100	AGE 6-12 MONTHS			AGE 1-10 YEARS		
	CELIAC DISEASE			CELIAC DISEASE		
	STEATORRHEA	NO STEATORRHEA	CONTROLS	STEATORRHEA	NO STEATORRHEA	CONTROLS
0–20	6	10	3	17	26	5
20–40	0	0	6	7	10	3
40–60	0	0	1	0	1	6
60–80	0	0	3	1	1	4
80–100	0	0	0	0	2	4
100+	0	0	1	1	0	13
Total	6	10	14	26	40	35

The frequency of gastric hypoacidity in celiac disease and the lack of correlation between gastric acidity and the presence of steatorrhea are shown graphically in Fig. 11.

The influence of the gastric acid on the value of amylase was first suspected because of several instances in which an initial determination, made when the patient was marasmic, showed a moderate concentration of amylase, while a subsequent determination, made after marked clinical improvement, gave a value of zero. It was subsequently found that the reverse was sometimes true of the free and total acid of the gastric juice (Table VI). This hypothesis was confirmed in a somewhat complicated experiment in which pure salivary secretion, gastric juice, and duodenal juice were obtained from a patient with celiac disease who lacked free gastric acid and from a control patient with a central nervous system disorder who had never suffered digestive difficulties. The values for amylase from these three sources and from both patients were compared and it was then shown that the control gastric juice had the power to destroy amylase, that this power was lost after neutralization, and that the neutral gastric juice

TABLE VI. CHANGE IN GASTRIC JUICE WITH CLINICAL IMPROVEMENT IN PATIENTS WITH CELIAC DISEASE

PATIENT	AGE	VOLUME (C.C.)	FREE ACID UNITS	TOTAL ACID UNITS
D. C.	1½ years	32	19	59
	3½ years	54	42	87
J. M.	1 1/12 years	3	0	29
	1 7/12 years	32	20	58
C. M.	9 months	11	5	15
	10 months	51	12	35
J. F.	7 months	10	0	25
	9 months	20	0	33

TABLE VII. COMPARISON OF AMYLASE FROM VARIOUS SOURCES IN A SEVERE CASE OF CELIAC DISEASE AND A CONTROL CASE

SOURCE	M. M., AGE 18 MO. CELIAC DISEASE (AMYLASE UNITS/C.C.)	J. M., AGE 24 MO. CONTROL (AMYLASE UNITS/C.C.)
Saliva	625	745
Gastric juice	60	0
Duodenal juice	32	152
Blood	0	Mean of controls 0.15

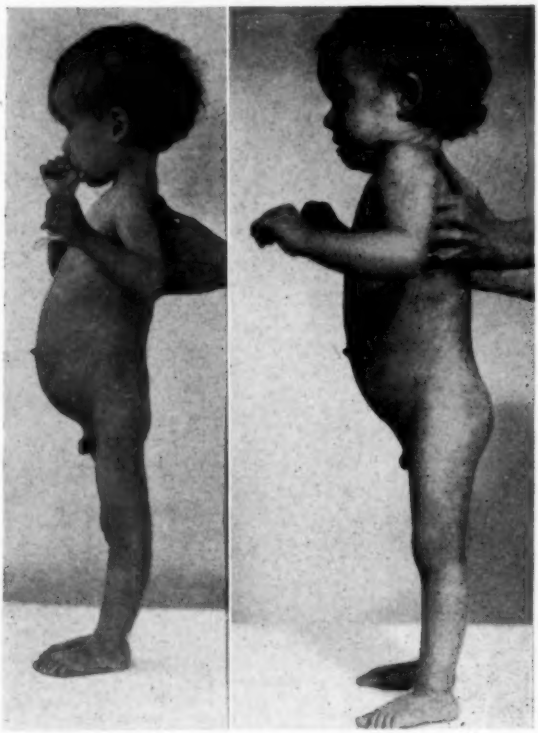
TABLE VIII. EFFECT OF GASTRIC JUICE ON DUODENAL AMYLASE

SOURCE	DUODENAL JUICE, AMYLASE UNITS/C.C.	
	M. M., CELIAC DISEASE	J. M., CONTROL
Duodenal juice	32	152
Incubated 10 minutes with M. M.'s gastric juice	38	158
Same with J. M.'s gastric juice	0	0
Same with J. M.'s neutralized gastric juice	35	127

of the celiac patient lacked the power to destroy this enzyme. The data of this experiment are presented in Tables VII and VIII.

The examination of the feces for starch also presents some difficulties. The method which has been found most useful is the traditional one of microscopic examination of a smear of a fresh sample stained with Lugol's solution. Specimens which have remained at body temperature or at room temperature for twenty-four hours or more often fail to show starch, even when this was present in the fresh specimen, presumably because of digestion by bacteria. Consequently, negative findings in a sample obtained after a day or two of constipation should be disregarded and all samples should be examined before they are many hours old. A distinction should be made between iodine-staining material within vegetable or banana cells and the finer extracellular granules which are not protected by a cell membrane. The intracellular granules are normally present in the feces of infants and young children. It is reasonable to explain the survival of undigested starch on the basis of protection by the cell membrane from enzymatic and bacterial action. Extracellular granules are not found in any considerable quantity in the feces of normal infants over 6 months of age and are abundant in the feces of children with celiac disease or starch intolerance with or without steatorrhea who have been fed cereal starch or potato. Elimination of these foods from the diet results in the disappearance of extracellular starch from the feces of these patients. It appears, therefore, that in the absence of pancreatic amylase some of the ingested starch which is unprotected by a cell membrane can escape digestion throughout passage of the intestinal tract. The presence of this starch may be presumed to contribute directly or indirectly to the production of other abnormalities of the feces which are characteristic of the disease, such as the foamy fermented appearance, acid reaction, and the alterations of the fecal flora in favor of gram-positive cocci, which are known to occur. As an illustration it may be mentioned that yeast cells having the morphology of

Monilia and staining with iodine are frequently seen in samples of feces which contain much extracellular starch and are rarely encountered otherwise; their presence is thus of some diagnostic value. The microscopic examination of the feces for starch is therefore a brief, simple, and, if due precautions are observed, a reliable diagnostic aid.



A. *B.*

Fig. 9.—J. B. *A*, At 18 months. *B*, At 20 months. On admission, the feces contained only 22.5 per cent fat on a dried basis. In spite of absence of steatorrhea, the physical appearance and weight curves are similar to those of the previous patients.

Whether the failure to digest starch and the consequent abnormalities of the intestinal contents and of the feces can in some way lead to deficiency of the vitamin B complex remains to be investigated. Past observations on the intestinal flora in celiac disease have contributed the information that enteric pathogens are usually absent but that the flora are altered. With the newer concepts of the role of intestinal bacteria in the formation and destruction of vitamins and with the evidence here presented that undigested starch is present in the intestine and may be assumed to alter the characteristics of the intestinal contents as a culture medium, the question of the role of intestinal bacteria in celiac disease should be reopened.

The evidence relating to starch indigestion in celiac disease has been presented in some detail because it is at present well supported by laboratory and clinical evidence; it also has immediate practical application in the diagnosis and treatment of the disease. Close observation of patients has yielded fragments of evidence that the basic disease has more attributes than lack of amylase secretion and consequent failure to hydrolyze starch. There is an almost universal clinical response to a high protein diet and a tendency to hypoproteinemia on a diet which contains protein at levels which are adequate for normal infants.

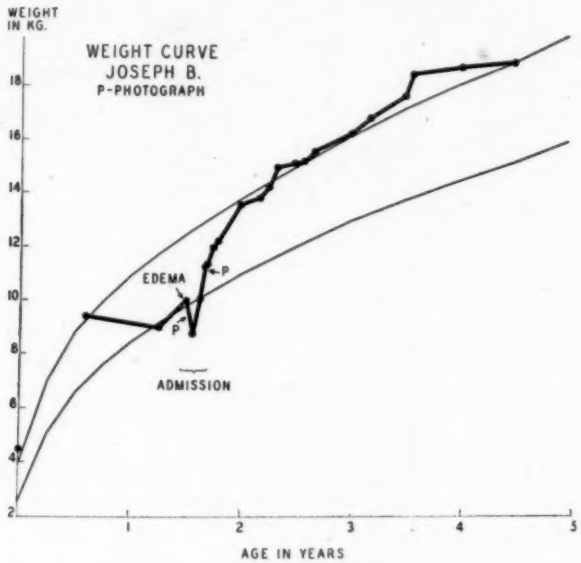


Fig. 10.—J. B. Weight curve.

This cannot be explained on the basis of a loss of nitrogen in the feces, for according to our data this is usually within normal range. It has recently been reported that amino acid absorption is normal in celiac disease.[7] There is therefore indirect evidence of a defect in protein metabolism in most, if not all cases; it is not yet clear whether this is a necessary part of the basic constitutional defect.

There are a number of other abnormalities which are commonly but not universally present, the relationship of which to the disease is not yet clear. Some of these are enumerated as follows:

1. Gastric hypoacidity and sometimes hypochylia. This is as common in mild as in severe cases. In many instances it has been reversible.

2. A variety of types of anemia, significantly more common in cases with gastric hypoacidity. This is probably a secondary phenomenon.

3. Abnormal gastrointestinal motility with evidence of a "deficiency pattern," demonstrable by serial roentgenograms following a barium meal.

4. Osteoporosis and delay in bone maturation in the presence of normal levels of serum calcium and phosphorus and in the absence of rickets.

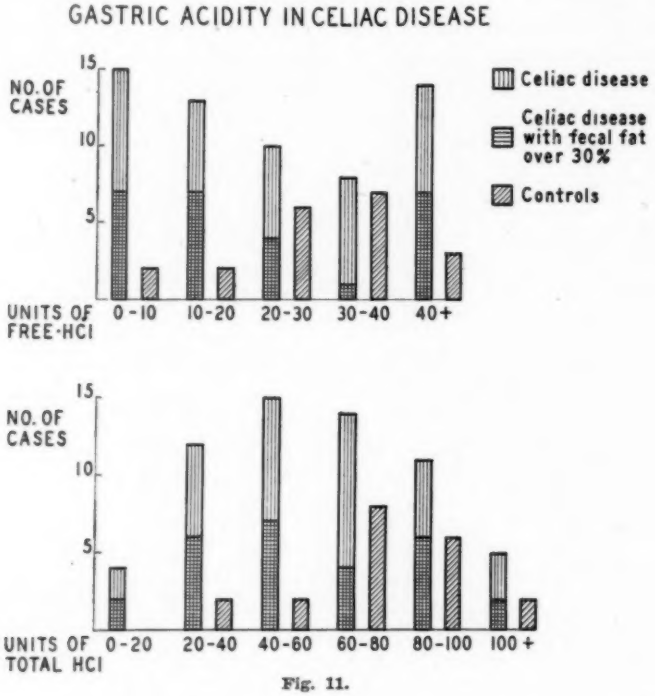


Fig. 11.

Because of the recent suggestion that celiac disease is the result of gastrointestinal allergy[8] our experience in this regard should be mentioned. Among eighty-one records of the present series, fourteen have been have been found with a history of allergy as defined by the presence of asthma, hay fever, severe eczema or proved gastrointestinal allergy. Of these, nine were considered to have major allergy. Two had normal levels of amylase and probably do not have celiac disease on a basis of starch intolerance. They may be said to present the celiac syndrome on the basis of gastrointestinal allergy. In the remaining sixty-seven charts of the present series, evidence of allergy in the patient has been absent or unconvincing. This incidence is not significantly greater than has sometimes been estimated for the general populace.

The evidence which has been presented that the steatorrhea of celiac disease is a transitory and inconstant phenomenon while difficulty in starch digestion is a constant finding which persists at least during the first five years of life, gives us a new background for the evaluation of the various regimes popular in the past. The diet which was devised about five years ago for

patients with starch intolerance and has proved successful in these patients and in those who have recovered from the acute steatorrheal phase of celiac disease does not differ greatly from some of the traditional ones arrived at empirically. Its characteristics are as follows:

1. It is high in protein, supplied as meat, cheese, egg, fish, and milk. Protein milk is given the younger patients and those recently recovered from the critical phase, while the majority of the others do well on whole milk.

2. Limited amounts of fat are given to young infants and to those recently recovered from a crisis. Moderate amounts are supplied to patients in good condition in the form of whole milk, butter and bacon. An excess of fat is avoided and fried foods are prohibited.

3. Carbohydrate is given in abundance and is supplied as simple sugars or disaccharides. Glucose, bananas, and fruit juices are the usual sources in the case of more severely ill patients. Cooked vegetables and raw apples and pears are soon added. Cane sugar is tolerated well within a few weeks of recovery from the acute phase. Care is taken to distribute the sugar throughout the day so that an excessive amount at any one meal is avoided. Cereal starches, bread, and potatoes are withheld for a year or more after recovery from the severe symptoms and are then given cautiously and in limited amounts.

4. Vitamin supplements include ascorbic acid, a fish liver oil concentrate, and vitamin B complex, all given orally. The preparation of vitamin B complex is selected not only for its thiamin content but on the basis of whether it contains the estimated daily requirements of pyridoxin, riboflavin, nicotinamide, calcium pantothenate, and folic acid. The daily dose has been designed to provide at least double the estimated daily adult requirement of these substances. No parenteral vitamin therapy is given, except in certain cases of severe anemia, in which liver extract is injected intramuscularly three times a week for a period of a few weeks.

A diet based upon these principles can be made varied and general and is usually well taken. It has been successfully applied to well over 100 patients. A patient with celiac disease when on this regime no longer has the characteristic stools, although the bulk may sometimes decrease only gradually. There may be a few loose stools on the first day or two of an acute respiratory infection, but this mild diarrhea responds either to a few days of restricted diet or to the administration of sulfonamides without alteration of the diet. The premature addition of bread, crackers, or other starch will result in resumption of loose pale stools after an interval of a day to several weeks or with the next upper respiratory infection. The relationship of starch ingestion to the abnormal stools is clearly shown in some of the cases: one boy regularly had loose stools on Mondays, following the Sunday visit to his grandmother. Another example is the patient R. T., reported here, who failed to respond to vitamin therapy while on a diet high in starch but responded promptly when dietary therapy was also given.

SUMMARY

The classical picture of celiac disease is believed to result from a deficiency of multiple nutritional factors complicating and resulting from a basic constitutional disease. The steatorrhea of celiac disease is transitory, and with intensive vitamin and dietary therapy it disappears within two months; it is viewed as a complication of celiac disease due to a specific deficiency and comparable in this regard to rickets or scurvy. A consistent and objectively demonstrable characteristic of the basic disease is a deficiency of pancreatic amylase, associated with an excess of starch in the feces when starch is fed and clinical intolerance to dietary starch. In uncomplicated cases the presenting symptom is the occurrence of repeated bouts of diarrhea with large, foul, pale, foamy stools and an enlarged abdomen. These bouts are usually initiated by an upper respiratory infection. The symptoms respond to a diet high in protein, low in starch, and abundant in vitamins. The classical picture of celiac disease with steatorrhea is the result of a multiple deficiency state superimposed on the basic disease under adverse circumstances. An attempt is made to evaluate other phenomena of the disease with respect to whether they are part of the primary defect or a result of secondary nutritional deficiency. There is suggestive evidence that the difficulty in protein metabolism, shown by the high requirement for dietary protein and a tendency to hypoproteinemia on a normal diet, may be an expression of the basic disease.

REFERENCES

1. Gee, S.: On the Coeliac Affection. St. Barth. Hosp. Rep. 24: 17, 1888.
2. Herter, C. A.: On Infantilism from Chronic Intestinal Infection, Characterized by the Over Growth and Persistence of Flora of the Nursling Period; a Study of the Clinical Course, Bacteriology, Chemistry and Therapeutics of Arrested Development in Infancy, New York, 1908, The Macmillan Company.
3. Fanconi, G.: Der intestinale Infantilismus und ähnliche Formen der chronischen Verdauungsstörung, Abhandl aus der Kinderheilk. und ihren Grenzgeb, Heft 21, 1928.
4. Hardwick, C.: Prognosis in Coeliac Disease; Review of 73 Cases, Arch. Dis. Childhood 14: 279, 1939.
5. Parsons, L. G.: Celiac disease; Rachford Memorial lectures, Am. J. Dis. Child. 43: 1293, 1932.
6. May, C. D., McCreary, J. F., and Blackfan, K. D.: Notes concerning cause and treatment of celiac disease, J. PEDIAT. 21: 289, 1942.
7. West, C. D., Wilson, J. L., and Eyles, R.: Blood Amino Nitrogen Levels; Changes in Blood Amino Nitrogen Levels Following Ingestion of Proteins and of a Protein Hydrolysate in Infants with Normal and with Deficient Pancreatic Function, Am. J. Dis. Child. 72: 251, 1946.
8. Kunstadter, R. H.: Gastrointestinal Allergy and the Celiac Syndrome, J. PEDIAT. 21: 193, 1942.

AN EVALUATION OF BENADRYL, PYRIBENZAMINE, AND OTHER SO-CALLED ANTIHISTAMINIC DRUGS IN THE TREATMENT OF ALLERGY

BRET RATNER, M.D.
NEW YORK, N. Y.

THERE is more than one school of thought with respect to the genesis of hypersensitive phenomena. The toxic or anaphylatoxin theory was based on the assumption that an antigen to which an animal is sensitized, when reinjected, is split by proteolytic ferments into toxic degradation products which produce the now well-known symptoms characteristic of the hypersensitive state. This early concept was later modified by a substantial amount of evidence favoring the hypothesis that histamine is liberated from the tissues during the antigen-antibody inter-reaction, and that the symptoms of anaphylaxis and allergy are, therefore, directly attributable to the action of the released histamine. In recent years, the advocacy of this hypothesis by several staunch proponents has awakened a renewed interest in the search for chemical or biologic substances capable of abolishing or diminishing some or all of the effects of the released histamine.[1-6]

Hill and Martin,[7] in 1932, critically reviewed 165 substances or methods that might serve to inhibit anaphylaxis nonspecifically, and they came to the conclusion that none were ideal for the purpose. In the succeeding years, considerable additional experimentation was done, but the interpretation of results in most instances is open to question according to Feinberg[8] who reviewed much of it in 1944.

One of the first of this series was the enzyme, histaminase, which destroys histamine in vitro.[9] It was recommended for oral and parenteral use. Although it was received with great éclat and was enthusiastically advocated for the relief of all forms of allergy (under the trade name of Torantil), it soon found its resting place as another of the many ineffectual remedies.[10, 11]

Fell and his co-workers[12, 13] offered still another approach to the problem by developing a substance which became known as hapamine. It is a histamine-hapten combination with despeciated, normal, horse serum globulin. The underlying concept was that injections of this substance would produce antibodies against histamine and thus fortify the individual against the allergic symptoms induced by liberated histamine. The procedure proved unsound not only because it did not produce any immunity but because it induced sensitivity to the new hapten antigen in a number of instances.

We are now in the throes of experimenting with a new series of so-called antihistaminic drugs. The two drugs most widely advocated are Benadryl, a Parke, Davis product which was studied by Loew and associates,[14-16] and Wells and associates,[17, 18] and Pyribenzamine, a Ciba product reported upon by

From the Department of Pediatrics, New York University College of Medicine.
Presented before the Fifteenth Annual Meeting of the American Academy of Pediatrics, Pittsburgh, Pa., Feb. 24-27, 1947.

Mayer.[19, 20] News of the experimental and clinical investigations was catapulted upon the public and medical profession alike through the medium of the lay press, including the *Saturday Evening Post, Life,* and newspapers throughout the country.

These new synthetic chemical formulas are complex structures involving the benezene rings. Benadryl is β-dimethyl-aminoethyl benzhydryl ether hydrochloride. Pyribenzamine is N-pyridil-N-benzyl-N-dimethylethylenediamine monohydrochloride.

From a historic viewpoint, it may be of interest to know that these drugs were preceded by numerous compounds chiefly of French lineage, e.g., 929 F and 1571 F,[21-23] and 2339 R. P., known as Antergan,[24] all having antihistaminic and antianaphylactic properties. Newer French preparations, such as compound 2786 R. P., known as neoantergan,[25] are less toxic and are attended with considerable clinical success according to the French literature. The story of the evolution of these drugs and an evaluation of them have been given in detail by Feinberg,[11, 40] Code,[26] and Mayer.[20]

Anthallan, another coal tar derivative, was introduced to the profession through a widespread presentation of its merits in the lay press, and through a clinical analysis by Ghiselin.[27] The *Journal of the American Medical Association,* commenting editorially on the Ghiselin study,[28] stated: "Notably lacking in this report are parallel studies on control patients, or, in fact, any controls whatsoever." Final judgment on the value of anthallan must be deferred.

PHARMACOLOGIC ACTION

According to some investigators,[14-24, 29] pharmacologic studies suggest that these antihistaminic drugs have three important actions. They alleviate (1) smooth muscle spasm, (2) bronchial constriction caused by histamine or anaphylactic shock, and (3) vasodepressor effects of histamine.

From the fact that they counteract the spasmogenic effects of barium chloride and acetylcholine, it has been concluded that these drugs must also possess a musculotropic, antispasmodic action and neurotropic effects (atropine-like). Epstein[30] believes that these drugs must possess additional pharmacologic qualities as evidenced by their sedative effect.

During prolonged drug administration in dogs, no progressive changes were noted in the blood counts, hemoglobin, and nonprotein nitrogen values. The differential blood counts also remained at levels close to those of the pretreatment period. Histologic studies showed no evidence of acute or chronic degenerative processes in any of the organs. The choroid plexus, however, appeared somewhat more congested than usual.[31]

Reinstein and McGavack[32] found that unlike the epinephrine type compounds, benadryl does not produce an increase in pulse rate and blood pressure in man, but, on the contrary, lowers blood pressure and causes drowsiness. Benadryl given by mouth has no apparent effect on glucose tolerance. When given intravenously it appears to increase sugar tolerance, a phenomenon which may be mediated through the liver. Friedlaender and Feinberg[33] also noted a fall in blood pressure.

McElin and Horton[34] showed that the action of benadryl on gastric secretion in man is somewhat inconsistent; only in some instances was the ability to block the gastric response to histamine demonstrated.

The effects of these drugs in reducing urticaria, drying up the secretions of hay fever, and producing dryness of the mouth may be due to the blocking of the secretagogue action of histamine. These activities may also be due to antihistaminic effects on blood vessels. The dryness of the mouth may be interpreted also as an atropine-like effect. Speculation concerning the drowsiness, disorientation, jitteriness, and many other profound influences on the upper brain centers would lead us far afield and without profit at this stage of our knowledge.

Friedlaender and Feinberg[33] did some valuable studies on experimental whealing in the human subject in relation to benadryl and pyribenzamine. They found that oral administration of either caused only a slight impairment in the development of experimentally produced histamine wheals. The direct local application to skin sites results for a limited time in a reduction of any histamine reaction subsequently produced in that site. This effect may also be obtained by combining the antagonist directly with the histamine solution. An almost identical action was obtained on ragweed-tested wheals, wheals produced by codeine, morphine, atropine, pilocarpine, physostigmine, and bee venom on skin sites previously treated with the antagonist. Pyribenzamine appeared to have greater activity than benadryl.

Arbesman and associates[35] found that pyribenzamine given orally reduced the size of histamine wheals in eighteen of twenty-eight subjects and reduced skin reactivity in fourteen of twenty-four allergic patients. Such oral administration also reduced the reactivity of skin sites passively sensitized with a serum containing cottonseed reagins.

Passage Through Breast Milk and Placenta.—A patient seen with Dr. Harold J. Eisenberg of New Rochelle is of interest because of the suggestive demonstration of the passage of these drugs through the breast milk.[36]

> A nursing mother was given 50 mg. of benadryl every three hours to relieve a contact dermatitis. After the third dose it was observed that the breast-fed infant, 5 weeks old and normal in every respect, became quite lethargic. However, therapy was not discontinued until three days later, when the lethargy and constipation of the infant became very marked. The infant was then taken off the breast and placed on an evaporated milk formula. Twenty-four hours later, the infant's symptoms all disappeared.

I have little doubt that these drugs will show an equal or greater readiness to pass through the placenta because of the great permeability of the placental barrier.[37]

MODE OF ACTION OF BENADRYL AND PYRIBENZAMINE

Although these drugs are said to be antihistaminic, proof for such a concept is by indirection. As Code[26] has pointed out, because benadryl relieves symptoms is not conclusive proof that these symptoms are due to histamine. The contention of Loew and Kaiser[14] is: "In view of the fact that these synthetic benzhydryl ethers are effective in alleviating both histamine shock

and anaphylactic shock, the data constitute additional *indirect* evidence that the chief symptoms of anaphylaxis are referable to histamine."

Wells and his associates[18] express the belief that the chemical structure of benadryl (β-dimethyl-amino-ethyl-benzhydryl ether) suggests that direct chemical interaction with histamine is improbable. They imply that if benadryl or pyribenzamine combines with the receptive substance, it prevents the histamine from combining at the same site. This mode of drug antagonism is demonstrated also in the competition between para-aminobenzoic acid and sulfonamides, atropine and acetylcholine, and ergotoxine and epinephrine.

Further pharmacologic studies with benadryl by Loew and associates[38] lead them to conclude: (1) histamine is not inactivated because of chemical union or neutralization, for if it were so, one would expect greater antagonism of the gastric secretagogue action of histamine; (2) benadryl does not neutralize histamine stoichiometrically, because a four-times weaker dilution of benadryl than that of histamine prevented the spasmogenic action of the latter; (3) because benadryl prevented the spasmogenic action of barium and acetylcholine on intestinal smooth muscle, it is unlikely that benadryl chemically neutralizes such dissimilar substances as histamine, barium, and acetylcholine; (4) the antagonism toward these substances suggests the more probable explanation that the drug alters the permeability of smooth muscle or combines with some portion of the effector cell so as to prevent histamine or other spasmogenic agents from producing a normal response.

Halpern[24] is of the opinion that these drugs so modify the reaction of the allergically affected organ that histamine is incapable of exercising its customary effect. They do not prevent the liberation of histamine or increase its destruction. This conclusion is supported by the observation of Wells and associates,[17] who show that benadryl does not materially interfere with the release of histamine during anaphylactic shock in dogs.

In view of this and other evidence[20] that these drugs do not inactivate histamine because of chemical union or neutralization, it would seem more logical at this point to attribute to these drugs the capacity to counteract the musculotropic effect of antigen-antibody or histamine reactions, rather than to describe them as antihistaminic or competitive drugs.

A study by Curry[39] has just been published, which casts further doubt on the assumption that these drugs are specifically antihistaminic, or that they differ too markedly from other antispasmodic drugs in their action. He investigated the effects of bronchoconstriction resulting from the intravenous injection of histamine in human beings by an ingenious method. He found that benadryl, pyribenzamine, atropine sulfate, aminophylline, epinephrine, and ephedrine all gave protection against histamine bronchoconstriction.

Despite the finding that benadryl and pyribenzamine do interfere with anaphylaxis and histamine shock in guinea pigs and dogs if given in large amounts, they have been signally ineffectual in relieving asthma. The conclusion which should be drawn from the anaphylaxis studies of Wells, Morris, and Dragstedt,[17] Loew and Kaiser,[14] and Mayer,[20] is that these drugs alleviate

anaphylactic shock somewhat when given in large doses, but do not afford real and unquestioned protection of a constant and high degree.

Mayer[20] asserts: "The challenge of these substances is that they should enable us to test, extend, or restrict the histamine theory of allergy."

From their mode of action it is obvious that these drugs can act only as palliative agents and do not eliminate the basic mechanism responsible for allergic symptomatology.

CLINICAL EVALUATION OF THE SO-CALLED ANTIHISTAMINIC DRUGS

It is well nigh impossible to evaluate the efficacy of any drug in allergic diseases with any degree of accuracy, because: (1) the criteria for measuring the benefits are not uniform and are for the most part subjective; (2) the ingestion or injection of any medicament whatsoever may bring temporary relief, because we must recognize that psychogenic influences often play an important part; (3) spontaneous desensitization to antigens may occur; and (4) the symptoms of allergic episodes are self-limited and may be receding in severity just at the time the drug is tried.

I have read over 100 articles on this subject, and cannot help but feel how wise it would have been if the observations had been withheld for a longer period. A longer experience with these drugs might have given a better perspective. I have tried to be as objective as possible in the perusal of these papers, to present, if possible, an unbiased picture, and have steadfastly attempted to veer away from personal observations in the evaluation of these drugs. It is unfortunate that all of the papers cannot be mentioned, but it would be impractical to cope with them. For the most part they would merely serve to corroborate the viewpoints expressed herein. The literature is already large and new papers are appearing at a rapid rate which is evidence of the great interest which these drugs have aroused.

Judged solely from the literature of the pharmaceutical firms marketing these drugs, they are truly remarkable. The percentage of improvement from their use in the various conditions might be summed up as follows[31]:

Urticaria	95 per cent
Vasomotor rhinitis	77 per cent
Eczema	63 per cent
Hay fever	85 per cent
Asthma	64 per cent
Migraine	66 per cent
Angioneurotic edema	86 per cent
Atopic dermatitis	64 per cent
Pruritus	75 per cent
Erythema multiforme	79 per cent
Dermographia	75 per cent
Food allergy	87 per cent
Contact dermatitis	78 per cent
Physical allergy	64 per cent
Penicillin reactions	97 per cent
Drug reactions	92 per cent
Reactions to biologics	100 per cent
Dysmenorrhea	87 per cent

In published clinical reports, there is wide variance of figures given by the same authors in successive papers.

I confess that I find it difficult to appraise the observations, and must take recourse in presenting the individual evaluation of the various authors, rather than to attempt to make a summation, giving a clear-cut appraisal, as has been done by the pharamaceutical firms.

One conclusion can be drawn. These new pharmaceutical discoveries fall short of the wonder of the newer antibiotic substances, and hence cannot compete with the latter for recognition as truly great advances in medicine. After only one year, we know that these drugs do not cure or eradicate allergy. They are an addition to a long line of palliative remedial agents.

DOSAGE

As a rule, benadryl is dispensed in capsules of 50 mg. each, but it may also be prescribed as an elixir, each teaspoonful containing 10 mg. Pyribenzamine is dispensed in 50 mg. scored tablets. Manufacturers advise against biting or chewing the tablets because of the local anesthetic action and bitter taste.

The recommended oral dose for young children is 2 mg. per pound, the total to be divided into two to four doses.[41] The contents of the capsule may be mixed with syrup or jelly. The average dose orally for older children and adults is 50 mg. three or four times daily.

Benadryl has been suggested for intravenous or intramuscular use in solutions of 10 to 20 mg. per cubic centimeter. However, intravenous administration of pyribenzamine is not recommended.[42] Laboratory experiments show that such administration of 1 mg. per kilogram or more in dogs usually results in acute hypotension which lasts for about ten minutes. McElin and Horton[34] found that benadryl given intramuscularly causes pain with erythema, induration, and tenderness.

For nasal use, even a 0.5 per cent solution was found to be too irritating.[33]

These drugs have been given in doses as high as 600 mg. orally per day without obvious ill effect. Curtis and Owens[43] observed three patients who were given benadryl for two, six, and seven months respectively, with no ill effects.

Logan[41] suggests that if no effects are noted in thirty to forty minutes the dose is inadequate and larger doses may be effective. However, I believe that one should be cautious in adopting such a procedure in asthma, for example. It would seem wiser to resort to epinephrine or aminophylline.

The maximum response occurs in about twenty to sixty minutes after oral administration and generally lasts for several hours.

URTICARIA

These drugs were first heralded to the American medical profession by Curtis and Owens in 1945,[43] and they were also reported upon clinically in the same year by Shaffer and associates[44] as beneficial in the alleviation of urticaria and angioneurotic edema.

Feinberg and Friedlaender[50] recommended benadryl and pyribenzamine as being equally efficacious in various types of urticarial skin disorders. Where a sedative effect is desired, they suggest the use of the former, and in those cases in which higher doses are needed, the latter. They also noted that relief was obtained by many patients with chronic urticaria in whom other measures failed. In serum sickness following the use of penicillin, the skin lesions were controlled but the joint involvement was not dramatically affected in the majority.

The percentage of good results varies with different investigators, but the majority attest to its value in over 80 per cent of patients suffering from this syndrome. Itching is relieved first, then the swelling and erythema disappear. Often, although the patient is relieved of the itching, the swellings of unusual size still remain.

Schwartz and Levin[51] state that acute wheals disappear within twenty minutes to one hour in their experience, whereas the symptoms can be turned on and off at will by giving or withholding the drug in cases of chronic urticaria.

Logan[41] adds an interesting observation of the effect in a 2-year-old child who had urticaria for three weeks without determining its etiology. After the first dose of 10 mg. the hives disappeared in thirty minutes. The medication was continued for two days and then stopped. For twenty-four hours the urticaria was absent, then recurred, and has since recurred whenever the medication was stopped.

Feinberg[11] further emphasizes this observation by stating that in urticaria and "serum-sickness" reactions the relief is apparent for only a few hours following each dose of the medicament and that the final course of the ailment is in no way shortened or affected by this therapy. One never knows when a spontaneous recession will occur. Barefoot and associates[49] rightly point out that it is difficult to evaluate the therapeutic value of benadryl and pyribenzamine in acute urticaria because many patients would be asymptomatic within a few days without any form of therapy.

These drugs do not eradicate the underlying cause of urticaria, the antigen-antibody interreaction, and episodes do recur. Levin's[45] statement is of interest, therefore. He found that they were excellent for children with acute urticaria and noted that relief occurred as promptly as with epinephrine. Hence, in patients who in the past required several injections per day for several days, they may prove to be a good substitute because they can be administered orally.

Curtis and Owens[43] gave benadryl for periods of two, six, and seven months respectively to three patients with urticaria, without ill effects. They believe that symptomatic relief can be afforded for many months in cases in which the etiologic cause is unknown.

In severe or chronic cases these drugs may be valueless.

Todd[48] has worked out an interesting group of urticarial situations (to which we have added a few) in which benadryl and pyribenzamine may be of benefit:

1. In patients exhibiting generalized nonspecific irritability of the skin, which is subclinical but becomes manifest when attempting to do routine skin tests.
2. In maintaining the urticaria patient in comfort for a few weeks until specific desensitization becomes effective.
3. In controlling the urticaria following liver injections and penicillin (orally or by injection) and other biologicals and antibiotics.
4. In controlling urticaria and angioneurotic edema of serum sickness.
5. In relieving both allergic antigen-antibody whealing and nonallergic urticaria.
6. In relieving promptly the whealing reactions to larva migrans, Black Flag, D. D. T., and other insect, parasitic, and chemical irritants.
7. In dermographism.
8. In poison ivy.
9. In urticarial dermatoses caused by barbiturate compounds and other drugs.
10. In pruritus ani and vulvae.

SERUM SICKNESS AND ANAPHYLACTIC SHOCK

In serum sickness, the relief is apparent for only a few hours following each dose of these drugs. The itching is relieved promptly and the lesions are kept in abeyance in the majority of cases. It is difficult to ascertain, however, whether the final course of the ailment is in any way shortened or otherwise affected by this therapy.

The value of benadryl in a severe case of accelerated serum sickness is exemplified in a report by Bowen.[52]

A child of 2 years was given 1,500 units of tetanus antitoxin subcutaneously. Forty-eight hours later he had violent urticaria and three days later the edema was so massive, and by the sixth day the respiratory difficulty so critical, that a bad prognosis was given the parents. All emergency measures had been tried, including epinephrine in oil and aqueous solutions and glucose intravenously. At 5 P.M. of the seventh day, when the child's condition appeared hopeless, 100 mg. of benadryl was given by mouth, followed by 50 mg. every four hours for four doses, then every six hours for twenty-four hours. Three days later the child was discharged, completely well.

A 9-year-old female patient experienced an anaphylactic shock reaction in the course of protein skin testing by Drs. Samuel Untracht and Frederick Hertzmark on our pediatric service at Sea View Hospital.

After 0.02 c.c. of horse serum and 0.02 c.c. of dust extract had been given intracutaneously on two separate sites on the forearm, the patient developed an immediate large local reaction at each site. Within a few minutes generalized urticaria spread over the entire body and angioneurotic edema involved the face and upper and lower extremities. This was diagnosed as a systemic anaphylactic reaction to the test materials. Moderate but typical sibilant râles were heard in the chest. The child was given 3 minims of epinephrine five minutes after the reaction. Her condition became progressively worse, with marked itching and exaggeration of the urticaria, and angioneurotic edema completely closed her eyes. Massive edema was evident in her hands and feet. About an hour after the reaction occurred, 50 mg. of benadryl was given. The patient became drowsy within a few minutes. The itching gradually subsided, even though the urticaria became more pronounced, and she appeared comfortable. Two hours later, 100 mg. was administered and the child slept through the night. Benadryl, in 50 mg. doses, was repeated three times a day for the next two days. On the third day the condition had cleared completely.

This dermal type of anaphylactic reaction apparently responds well to benadryl. The fact that 3 minims of epinephrine were given promptly may have altered the respiratory distress. I am not certain whether these drugs would act as brilliantly with a profound bronchiolar spasm characteristic of the guinea-pig type of anaphylaxis. But in our case, as in Bowen's, it certainly appears to have been of value in the edematous type of reaction.

It is interesting in contrast to present the case of a 5-year-old boy in another of our wards who developed an attack of asthma at about the same time as the episode described. When benadryl was administered to him he became drowsy, but progressed rapidly into a state of greater obstruction of respiration. He became cyanotic and appeared critically ill. Oxygen and aminophylline intravenously relieved him. It may be that the true asthmatic symptoms of anaphylaxis will not respond to these newer drugs as well as they do to epinephrine and aminophylline.

SEASONAL HAY FEVER

The majority of reports appear to be favorably disposed toward the use of these drugs with this syndrome.

Koelsche and associates[53] report 75 per cent of fifty-two patients relieved with benadryl. In a symposium[54] given recently, good results were variously indicated to be between 59 and 75 per cent of cases. Arbesman and associates[55] declare that as many as 84 per cent were benefited by the use of pyribenzamine. Logan[41] had twelve cases during the ragweed season with excellent or good results in nine. Of three with associated asthma, only one was helped. Eyerman's[47] figure is 67 per cent, and Bowen's[52] 60 per cent. Epstein[30] states that most of his pollen cases were benefited. Bowen had three cases in the mid-ragweed season who were amazingly relieved with benadryl. Feinberg and Friedlaender[56] report 82 per cent of 254 hay fever patients showed benefit.

However, Friedlaender[57] warns that unless rigid criteria are used to evaluate the beneficial results, overenthusiasm is the result. He believes that the majority of hay fever reports to date have not employed the criteria necessary to establish a firm basis for claims. Many unsubstantiated claims have been made in regard to other "cures" in the past, because there is so much dependence on subjective data. Friedlaender's criteria include daily pollen counts, prevailing atmospheric conditions, and control groups; with an evaluation on this basis, he was able to attribute improvement definitely to benadryl in but a small percentage of his cases. Doses of 50 to 200 mg. daily were employed in the majority of cases.

Feinberg[11] and Arbesman[55] suggest that pyribenzamine in combination with ephedrine or aminophylline is more effective. Relief from these drugs is usually noted after the first dose, but often several doses are required.

It has been reported that blockage of the nose is often aggravated by these drugs. They apparently work best in the watery type of hay fever. In patients who have used nasal constrictors too consistently and who have a blocked nose as a result, some have found that pyribenzamine and benadryl sometimes relieve the condition.

NONSEASONAL ALLERGIC RHINITIS

Reports are not in agreement with respect to the effectiveness of these drugs in nonseasonal allergic rhinitis. At a symposium of the American Academy of Allergy,[54] the reports varied from 28 to 85 per cent effectiveness.

Schwartz and Levin[51] found that either relief is obtained within one hour or no benefit is derived. Once relief is obtained, it is necessary in most cases to continue the drug every four hours because the action is only palliative.

Epstein[30] did not find the drugs very effective in cases due to dust or food sensitivity, and still less so in so-called intrinsic rhinitis in which external allergens cannot be demonstrated.

On the other hand, a report appears by Williams[58] who obtained relief in 90 per cent of ten patients with perennial vasomotor rhinitis. In hyperplastic ethmoiditis he also found a disappearance of polypoid tissue and a diminution of purulent discharge, but indicates that symptoms tend to return within twelve hours of cessation of dosage.

With equal assurance Eyerman[47] indicates that polyposis was not helped, and Bowen[52] states that less than 20 per cent of his vasomotor rhinitis patients, obtained relief.

Arbesman and associates[55] found that pyribenzamine relieved sneezing in rhinorrhea and nasal occlusion in 75 per cent of 313 patients with allergic rhinitis.

Feinberg and Friedlaender[56] noted benefits in 64 per cent of the cases with pyribenzamine, whereas Feinberg[59] observed such benefits in only 15 per cent of forty-seven cases with benadryl.

DERMATITIS

One of the admitted virtues of benadryl and pyribenzamine is their effectiveness in relieving pruritus. However, they have their greatest value in the milder forms of dermatitidies, not through any curative action, but because the relief from itching and scratching is frequently responsible for some improvement in the cutaneous lesions.

Feinberg[11] found that pyribenzamine relieved itching in sixteen out of twenty patients with acute and chronic atopic dermatitis, while benadryl was effective in twenty out of twenty-five similar cases. Contact dermatitis was less responsive. Waldbott[60] and Levin[45] obtained equally good results. Epstein,[30] however, found it difficult to evaluate their effectiveness in atopic dermatitis, and believed that only acute exacerbations were relieved, but not atopic dermatitis of long standing, contact dermatitis, or infectious eczema. He found that erythema multiforme was benefited. Pyribenzamine was more effective than benadryl in his experience.

Neurodermatitis and dyshidrotic eczema were unaffected,[44] as well as disseminated dermatophytide, severe local reaction to diphtheria toxoid, and pruritus with jaundice.[49]

A definite decrease in itching was noted in certain cases of contact dermatitis and poison ivy. Dermographism was reduced.[11, 52] Bowen believes that where you have edema and pruritus in juvenile eczema these drugs are frequently helpful in allaying pruritus.

MIGRAINE

The data with respect to the relief of migraine with these drugs are by no means consistent. Some claim that benefit is derived in allergic headaches, Ménière's syndrome, myalgia, and physical allergy of the head (Williams,[58] and McElin and Horton,[34]). Eyerman,[47] Bowen,[52] and Feinberg[11] find them of questionable value. If relief is to be obtained, at least 50 mg. every two hours are needed.

Levin[45] reports an aggrâvation of symptoms in two patients from benadryl.

ASTHMA

In this disease, which affects the majority of allergic children and adults, these drugs are of little real value. There is not the same consensus as with respect to the relief afforded in acute urticaria, seasonal hay fever, and pruritus.

Friedlaender and Feinberg[33] failed to secure any favorable results in twenty patients treated with benadryl, but observed benefit in two of twenty-five patients treated with pyribenzamine. Koelsche and associates[61] reported four of twelve patients improved. Schwartz and Levin[51] observed relief with benadryl in eight of twenty patients; attacks were diminished in severity, and some were completely improved after one or two days. In some cases patients reported aid from placebos. Bowen[52] found that less than 10 per cent of his patients were aided.

McElin and Horton[34] observed that coughing was made more difficult and the expectorated material seemed more tenacious. Epstein[30] also found the results disappointing with both benadryl and pyribenzamine.

Arbesman and associates,[35] however, claim that pyribenzamine prevented or relieved dyspnea and cough in 48 per cent of ninety-eight patients with asthma.

Waldbott[60] reports a favorable outcome with benadryl in a 7-month-old infant who had severe attacks of asthma occurring every ten days and lasting for ten to fifteen hours. On one occasion the infant was cyanosed and stuporous, with respirations of 80 to 90 and an imperceptible pulse. Attempts to relieve this attack by the usual methods were of little avail. However, a marked change in the child's condition ensued within one-half hour after 50 mg. of benadryl were given orally. The pulse rate dropped to 90 and respirations to 36. On two subsequent occasions the drug produced similarly good results. This author, on the other hand, quotes a patient with urticaria and asthma in which the first dose cleared the urticaria but left the asthma unabated, and cites three patients who developed asthmatic attacks shortly after the ingestion of benadryl.

Levin[45] also noted an aggravation of asthma in 3 per cent of his patients. In one instance, when 50 mg. were given to a patient in the office, a severe attack developed, requiring the administration of epinephrine. Two other patients complained of "choking up" within fifteen minutes, and a fourth patient had a marked aggravation of his attack. This author stresses the fact that asthma if infectious origin was not benefited by benadryl.

While treating patients with active pollinosis with 50 mg. of benadryl three to four times a day, Eyerman[47] noted that seven developed wheezing. Two were relieved with further treatment, whereas five were uninfluenced. He also found benadryl ineffective for severe bronchospasm. In two instances of idiosyncrasy to aspirin, bronchospasm increased and adrenalin was required. Benadryl was not efficient in any severe asthmatic episode, even with the oral administration of 100 mg.

In pollen asthma the nasal symptoms are often relieved but not the chest signs. However, the relief of nasal symptoms sometimes is reflected beneficially on the chest condition. Koelsche and associates[61] also noted improvement of hay fever symptoms but not the associated asthma.

Feinberg[11] obtained only 12 per cent favorable results with benadryl in a series of fifty patients with asthma, mainly of perennial etiology. Pyribenzamine was somewhat more effective than benadryl in 28 per cent of 121 patients with

asthma or allergic bronchial cough. But he points out that whatever benefit was derived from pyribenzamine orally, it was never comparable to the practically complete and rapid relief obtained with epinephrine hypodermically administered. Where relief was given it was usually only moderate. The spasmodic cough was more benefited than the dyspnea. He, too, noted that the asthma accompanying hay fever was seldom prevented by the use of either drug.

A drug that can dry up bronchial secretions and produce suffocation and choking sensations might very conceivably kill a patient if used during status asthmaticus. One can only conclude, therefore, that these drugs should be used with circumspection for severe asthma.

TOXIC AND UNTOWARD REACTIONS

Prior to the use of these drugs in the human subject,[14, 15, 19, 20, 31, 62] careful toxicologic studies were performed in albino mice, rats, rabbits, and dogs.

Toxicologic Studies in Animals.—The conclusion drawn from these studies was that benadryl and pyribenzamine have a low toxicity and are well tolerated by animals in many times the dosage recommended for man.

Death occurs in 50 per cent of albino mice after an oral dose of 167 mg. per kilogram, and in albino rats after 545 mg. per kilogram. Lethal doses are followed by violent excitement, convulsions, respiratory failure, and death in a few minutes to several hours. Excitement and ataxia occurred after nonlethal toxic doses and recovery followed in one to two hours.

From 10 to 60 mg. per kilogram was given orally to dogs for periods of thirty-seven to forty-nine days. No change was noted in eating habits, weight, blood counts, hemoglobin, or nonprotein nitrogen. No abnormal conditions were observed at autopsy, even after prolonged intake. Koepf and associates[63] gave pyribenzamine to dogs for one year in doses of 50 to 200 mg. daily with no alteration in the hematopoietic system, no impairment of liver or kidney, and no febrile reaction.

Toxicologic Studies in Human Beings.—According to some reports,[41, 63] these drugs have been given to human subjects for relatively long periods, 2, 3, 6, and 7 months respectively, without any obvious toxic effects.

Nevertheless, many reports have been made of side reactions that were not encountered in the animal studies. These seem to affect the higher brain centers more particularly. The most common complaint is drowsiness of some degree, which occurs more frequently after benadryl than pyribenzamine, approximately in 50 per cent of the cases with the former and 25 per cent with the latter. It is less marked in infants and children, even with large doses.[41, 45] However, in adults it may assume proportions only second to that from narcotics and anesthesia. Many cases of unconquerable somnolence have been encountered. Bowen[52] reports the case of a patient driving a car who failed to heed a red traffic signal and was arrested for being intoxicated, a "benadryl jag." Collisions with serious mishaps have been reported as a sequel. Slater and Francis[64] published a case report of a near fatal accident in a patient after only one 50

mg. tablet. One story is told of the doctor who took six capsules a day, and one day had to be awakened by a patient in the midst of a conference when sleep overcame him.

The effect of drowsiness is excellent therapeutically in pruritus and hay fever if the drug is given at bedtime. Some of the most beneficent effects must be attributed perhaps to this side effect. But we must recognize that if these drugs are given to an asthmatic they may in certain instances be as dangerous as morphine.

We are told that the drowsiness can be overcome with coffee, caffeine, benzedrine, and ephedrine. If this symptom occurs with each dose, medication may have to be discontinued. In some instances, however, this effect wears off rapidly.

Other side effects are dizziness, weakness, dilated pupils, dry mouth, nervousness, tingling of hands, tinnitus, nausea, vomiting, headache, and mental incoordination. Schwartz and Levin[51] report a patient with the sensation of "walking on air," McElin and Horton[34] report several with difficulty in coordination, O'Leary and Farber[46] report a patient with sensations of syncope. Williams[58] had patients who developed severe vertigo and were unable to continue working, and some mentioned difficulty in focusing their eyes.

Friedlaender[57] notes that pyribenzamine in large doses produces symptoms of cerebral stimulation, i.e., vertigo, nervousness, trembling, and insomnia, as frequently as drowsiness and lassitude.

In spite of the assurance from experimental data with respect to prolonged usage of the drugs without evidence of toxic effects, it appears to me to be too early to state finally that these drugs can be used without ultimate harm, judging from the case reports beginning to appear. A friend of mine who extolled the virtues of benadryl for his hay fever found after five weeks of constant use that he developed a persistent headache which lasted for two weeks. Another young person took forty capsules over a period of three weeks and became so weak that she had to remain in bed for one week and felt groggy and uncertain of herself for a week following her return to work.

Unusual Side Effects.—Reports of serious and unusual effects are filtering into the literature. Geiger, Rosenfield and Hartman[65] report a case of a shock-like reaction to benadryl.

> A white woman, aged 26, was being treated for a generalized seborrheic dermatitis of unknown origin. After receiving a total of 300 mg. of benadryl over a three-day period, she complained of palpitation, dimmed vision, malaise without drowsiness, and heartburn with nausea. Following the next 50 mg. tablet, the patient was found in bed unconscious, cold, pale, and pulseless. The blood pressure could not be read. Eyes were staring, but the pupils were equal and reacted to light. A solution of 7.5 minims of epinephrine (1:1,000) was given subcutaneously. Within thirty minutes the pulse was palpable, though weak, and the patient responded to painful stimuli. In three hours she was normal, with no recollection of what had happened. The following day magnesium soaks, supportive vitamins, and oral dosage of ephedrine were reinstituted and the patient continued to improve. On the eleventh hospital day the administration of benadryl was resumed, under careful observation. Again after 300 mg. over a period of three days, the patient began to complain of the symptoms noted on the previous occasion. She was somewhat disoriented and excited. The pulse was weak, the skin pale, but the blood pressure was normal. Benadryl was immediately discontinued and within two hours the patient felt entirely normal.

Unusual Symptoms of Cerebral Stimulation.—Symptoms of cerebral stimulation have been observed, such as difficulty of coordination,[34] muscular twitching,[60] narcolepsy, confusion, jitters, irritability[45] from benadryl, and vertigo, nervousness, trembling, and insomnia from pyribenzamine.[57] All are strikingly exaggerated in a case recounted by Weil.[66]

Benadryl was given for the relief of hay fever to a white boy, aged 3½ years, weighing 33 pounds. He had 50 mg. every morning and at bedtime for three days. On the third day he received 50 mg. just before he was put to bed. He went to sleep and his attitude was considered normal by the parents. At midnight the child awakened with a severe sneezing attack. He was given 100 mg. of benadryl and returned to bed. Twenty minutes later the child was sitting up in bed, singing, laughing, and "starry-eyed." He did not obey requests to lie down and to be quiet, but instead laughed and "acted as though he were drunk." At this time, muscular twitchings of the face and involuntary spastic movements of the extremities were first observed, and urinary incontinence followed. In about ten minutes (by which time Dr. Weil was in attendance) the involuntary muscular movements of the face and extremities were more pronounced and the child was irrational, not knowing where he was and not recognizing his parents. At this time he "dove from his bed to the floor." Although he landed on his head, he laughed as he was picked up and put back to bed. Physical examination was negative, except for: (1) muscular twitchings and purposeless movements of the extremities; (2) hypertonic patellar and triceps reflexes (corneal, cremasteric, and abdominal reflexes were considered normal); and (3) irrational speech gradually becoming slurred. Seconal, 1½ grains (0.09 Gm.), was administered by mouth, and within fifteen minutes the child was sleeping fitfully. Muscular twitchings and athetoid movements continued, and on moments of awakening the speech was slurred past the point of understandability. On several occasions in the next three hours the child attempted to "dive" out of bed again. About 4 A.M. the child sat up and spoke clearly but still showed evidence of muscular spasm and hypertonic reflexes. He fell asleep again and slept fitfully until 9 A.M. The effects of the seconal (?)—sleepiness, unsteadiness and anorexia—were evident until after the 2-to-4 P.M. nap. At 4 P.M., the child was examined again and considered normal. The reflexes were normal and conversation was rational. He had no recollection of the activity of the evening and early morning.

Again emphasizing the danger of marked mental disorientation from large dosage, particularly if self-medicated, is the case described by Borman.[67]

A convent nun, aged 18, suffered from ragweed sensitivity. She was given a prescription for forty-eight 50 mg. capsules of benadryl. She was decidedly relieved by them and consumed forty during the following forty-eight hours, a total of 2,000 mg. She became drowsy and acted queerly and disoriented. She dropped clean clothes into the laundry, left her tasks only partially completed, wandered off into other parts of the convent and did not remain in her bed at night. During instruction period she asked one of the sisters to pass the salt. For two nights she had "suffocating spells." Upon examination, her pulse, temperature, respirations, and blood pressure were normal. Within forty-eight hours after discontinuing the drug she made an apparently complete recovery.

To be sure, it may be claimed that the toxic effects herein described are not foreign to many good and valuable drugs, but such drugs are usually used for specific episodes over a definite period. My anxiety is due to the fact that here are drugs which are being prescribed not for a particular illness but for repeated use to relieve allergic symptoms which recur from time to time over many years. It has been amply demonstrated that their effect is purely palliative. The side effects might unquestionably result in accidental death. I have no doubt that

cases have already occurred. Take, for example, the child who runs out into the street after taking the drug; with judgment gone he might easily be run over. An individual in swimming might conceivably be so overcome by drowsiness as to drown. The child who "dove" off his bed, might with equal readiness dive out of the window. The nun walking in her sleep might be exposed to some precarious situation. A drug that can disorient an individual is certainly one to be used with caution.

COMMENT

The discovery of a single agent to combat the bewildering kaleidoscope of symptoms inherent in the allergy pattern has been the aim of chemists and pharmacologists, and the desire of practicing physicians.

Hay fever, asthma, urticaria, and eczema are but a few of the varied ways in which allergy manifests itself. The precipitating causes are even more numerous than the symptoms if one lists the foods, weeds, epidermals, drugs, bacteria, textiles, dusts, and organ products that have been found to be responsible offenders. The physician had to become so skilled in ferreting out these initiators of allergic symptoms that a new subspecialty of allergy has been developed in the fields of pediatrics, medicine, dermatology, and otolaryngology. It is to the "allergist" that physicians and patients turn for help in exploring this maze of cause and effect. After painstaking search the patient is taught the substances to avoid, and how to substitute harmless forms for the offenders, and in order to combat the onslaught of pollens he is compelled to take frequent desensitizing injections of the particular pollens to which he reacts.

Now, with the advent of the so-called antihistaminic drugs, the question arises, as to whether the procedures outlined are correct. Is there a drug that will dispel our allergic problem? Is that drug benadryl, pyribenzamine, or some one of the other new antihistaminic drugs which will undoubtedly be put out in competition? The underlying problem, of course, is this: has the histamine theory revealed the basic cause of allergy and given sharper definition to the universal pattern of allergy which is pointing the way to better treatment?

On the one hand, some believe that the major role in allergy is played by the interaction of antigen and antibody on sensitized tissue.[10] Others hold that the release of histamine is the direct and major cause of the allergic phenomenon. Dale[68] was the first investigator to voice this theory. He stated that anaphylactic shock is a result of cellular injury due to the intracellular reaction of antigen with aggregating antibody in the course of which histamine is released. To this released histamine he would attribute the symptomatology.

Dragstedt[4] contends that the pure cellular theory has no satisfactory explanation for the mechanism by which the antigen-antibody reaction produces the phenomena of anaphylactic shock. It seems to me that the proposition, first pointed out by Simonds and later supported by Wells, that the dominant symptoms in anaphylaxis, i.e., circulatory failure in the dog, bronchospasm in the guinea pig, cardiovascular failure in the rabbit, can all be brought into concordance on the basis of spastic contraction of smooth muscle in the various organs in which the sessile antibodies are found in greatest concentration.[10]

The question has been posed, how does the antigen-antibody reaction make the smooth muscle contract? One could counter by asking how does histamine make the smooth muscle contract. As a matter of fact, smooth muscle does contract when subjected to any one of many varied types of stimuli such as chemical and mechanical irritants, temperature changes, and reaction patterns established as "conditioned reflexes," as well as to antigen-antibody interaction or histamine. It is the nature of smooth muscle fiber to contract whenever stimulated; it can do nothing but contract and relax; such is its function.

Code[6] has suggested that histamine is liberated as a consequence of damage done within the sensitized cells, and it is this damage to the cell that is the fundamental etiologic factor in allergic or anaphylactic reactions. Liberation of histamine may be purely incidental. If the damaged cell happens to contain histamine, it will be liberated during the reaction. It must be conceded that if histamine is present in excessively large amounts it may contribute to the intoxication of the anaphylactic animal. However, the reaction takes place so rapidly as a rule that it is hard to believe that histamine can be liberated in sufficient quantity to account for immediate severe allergic reactions or anaphylactic death. On the other hand, Code[69] has shown that histamine is present in the blood of a dog in anaphylactic shock but it disappears after a relatively short time. It is difficult, therefore, to hold the histamine responsible for the anaphylactic death which may occur hours later when histamine is no longer demonstrable.

Actually, histamine release has not been demonstrated in allergy in man to the full satisfaction of all investigators. As a matter of fact, it has only been demonstrated in dogs and guinea pigs in severe anaphylaxis, but not in the rabbit, horse, or calf.[10]

To my mind, the asphyxial symptoms of asthma and a multitude of the minor allergic manifestations can be accounted for more plausibly by the disturbance of the physiology of a vital organ brought about by smooth muscle contraction which results from antigen-antibody interaction.

Where the stress is laid is a matter not only of academic but also of practical importance. To concede the value of a drug, such as benadryl or pyribenzamine, because it allays the symptoms of itching or a watery nose, is one matter. To accept drugs as important contributions in the fundamental treatment of allergy because they are said to be antihistaminic can only mean that we are ready to believe that histamine is the cause of allergy. The fact that these drugs relieve symptoms, as has already been said, is not conclusive proof that these symptoms are due to histamine. For my own part, I feel that we will require further and more convincing proof before such a conclusion may be drawn.

Much as we would desire it, I cannot conceive of a universal cure-all in allergy. The very nature of allergy, and its underlying antigen-antibody mechanism, precludes it. Were we to discover how to prevent the development of allergic antibodies, the problem would be settled. But the essence of allergic antibodies is the very essence of all antibodies. A substance that would

destroy all antibodies would obviously lead to a state incompatible with survival against noxious invading substances. The body must continually manufacture immunizing agents. The amelioration of allergy is based on the ability of the body to produce enough antibodies so that they may eventually reach the circulation and act as blocking or neutralizing bodies. Allergy is an ever-present battle against all types of foreign substances inhaled, ingested, or injected.

It is the study of the many ways and means that antigens have of invading the body and producing inter-reactions with tissue antibodies which offer the greatest hope for good and lasting results. The therapy of allergy must be viewed from a constitutional and preventive standpoint. It entails a search for all offending substances, their elimination or reduction, and a definite program for building up tolerance. The control of environmental excesses, highly antigenic food excesses, promiscuous and thoughtless use of sera and drugs, control of diseases which tend to increase the permeability and dysfunction of our protecting membranes, all tend to reduce the incidence of allergy. The problem rests heavily with the pediatrician because most allergies start in childhood. Don't think there is a short cut. For the present, there is no single drug or procedure that can do more than allay certain minor phases of the allergic symptomatology. Once the mechanism of a disease is understood, amelioration and possible eradication eventually follow. Were we to accept the histamine concept as the primary modus operandi of the allergic reaction, as I see it, there would be little hope for the control and prevention of allergy.

CONCLUSIONS

1. The release of histamine has not yet been proved to be the fundamental factor in anaphylaxis or allergic reactions, hence any therapy based on such a concept must be called into question.

2. Benadryl and pyribenzamine and other drugs of this group have not been proved to be antihistaminic, either chemically or pharmacologically.

3. These drugs have not proved of value in the eradication of allergic syndromes. They do not appear to prevent the entrance of antigen into the circulation and the antigen-antibody reaction from ensuing.

4. It is the nature of the allergic episode to be self-limited, and it is often spontaneously terminated without benefit of medical intervention. For this reason a wide variety of drugs seem to relieve it.

5. Benadryl and pyribenzamine are excellent compounds which alleviate symptoms of a widely diversified group of allergic conditions. It is significant that the greatest benefits are derived in acute urticaria and hay fever, in allaying pruritus, nasal and lachrymal discharges. They should take their place along with epinephrine, ephedrine, and atropine as excellent antispasmodics.

6. They are not as efficient in asthma and eczema, the more chronic and fixed syndromes, and should be used cautiously in the former.

7. These drugs must be used vigilantly because they may have serious side effects which in some cases may affect the higher brain centers.

8. These drugs deserve a place in our armamentarium as symptomatic remedies. My objection is that many physicians and more particularly lay

people, because of the widespread publicity, feel that they are cures. Furthermore, I feel that if we lay emphasis on palliative measures we will forget what is more important—that is, measures seeking to overcome the actual hypersensitivity of the patient. It is more important to look to the fundamental and basic principles underlying allergic phenomena, than to be content with mitigating measures. The latter may have a place during the period of investigation and initial treatment of a case, but certainly we should not be satisfied with that limited aim.

REFERENCES

1. Dale, H. H., and Laidlaw, P. P.: The Physiological Action of B-Imunazolylethylamine, J. Physiol. **41**: 318, 1910.
2. Dale, H. H.: The Anaphylactic Reaction of Plain Muscle in the Guinea Pig, J. Pharmacol. & Exper. Therap. **4**: 167, 1913.
3. Best, C. H., and McHenry, E. W.: Histamine, Physiol. Rev. **11**: 371, 1931.
4. Dragstedt, C. A.: Anaphylaxis, Physiol. Rev. **21**: 563, 1941.
5. Feldberg, W.: Histamine and Anaphylaxis, Ann. Rev. Physiol. **3**: 671, 1941.
6. Code, C. F.: The Mechanism of Anaphylactic and Allergic Reactions, Ann. Allergy **2**: 457, 1944.
7. Hill, J. H., and Martin, L.: A Review of Experimental Studies of Nonspecific Inhibition of Anaphylactic Shock, Medicine **11**: 141, 1932.
8. Feinberg, S. M.: Nonspecific inhibition of Anaphylaxis, Editorial, J. Allergy **15**: 302, 1944.
9. Best, C. H.: Disappearance of Histamine From Autolyzing Lung Tissue, J. Physiol. **67**: 256, 1929.
10. Ratner, B.: Allergy, Anaphylaxis and Immunotherapy, Baltimore, 1943, Williams and Wilkins Company.
11. Feinberg, S. M.: Histamine and Antihistaminic Agents, J. A. M. A. **132**: 702, 1946.
12. Sheldon, J. M., Fell, N., Johnston, J. H., and Howes, H.: A Clinical Study of Histamine Azoprotein in Allergic Disease, J. Allergy **13**: 18, 1941.
13. Fell, N., Rodney, G., and Marshall, D. E.: Synthesis and Immunologic Investigation. I. Histamine Azoprotein, J. Immunol. **47**: 237, 1943.
14. Loew, E., and Kaiser, M. E.: Alleviation of Anaphylactic Shock in Guinea Pigs With Synthetic Benzhydryl Alkamine Ethers, Proc. Soc. Exper. Biol. & Med. **58**: 235, 1945.
15. Loew, E. R., Kaiser, M. E., and Moore, V.: Synthetic Benzhydryl Alkamine Ethers Effective in Preventing Fatal Experimental Asthma in Guinea Pigs Exposed to Atomized Histamine, J. Pharmacol. & Exper. Therap. **83**: 120, 1945.
16. Loew, E. R., Kaiser, M. E., and Anderson, M.: Effect of Various Drugs on Experimental Asthma Produced in Guinea Pigs by Exposure to Atomized Histamine, J. Pharmacol. & Exper. Therap. **86**: 1, 1946.
17. Wells, J. A., Morris, H. C., and Dragstedt, C. A.: Modification of Anaphylaxis by Benadryl, Proc. Soc. Exper. Biol. & Med. **61**: 104, 1946.
18. Wells, J. A., Morris, H. C., Bull, H. B., and Dragstedt, C. A.: Observations on the Nature of the Antagonism of Histamine by B-dimethylaminoethyl Benzhydryl Ether (Benadryl), J. Pharmacol. & Exper. Therap. **85**: 122, 1945.
19. Mayer, R. L., Huttner, C. P., and Scholz, C. R.: Antihistaminic and Anaphylactic Activity of Some a-Pyridinoethylenediamines, Science **102**: 93, 1945.
20. Mayer, R. L.: Antihistaminic Substances With Special Reference to Pyribenzamine, J. Allergy **17**: 153, 1946.
21. Fourneau, E., et Bovet, D.: Recherches sur l'action sympathico-lytique d'un nouveau dérivé du dioxane, Arch. internat. de pharmacodyn. et de thérap. **46**: 178, 1933.
22. Staub, A. M., et Bovet, D.: Action de la thymoxyéthyldiéthylamine (929 F.) et des éthers phénoliques sur le choc anaphylactique du cobaye, Compt. rend. Soc. de biol. **125**: 818, 1937.
23. Staub, A. M.: Recherches sur quelques bases synthétiques antagonistes de l'histamine, Ann. Inst. Pasteur **63**: 400, 1939.
24. Halpern, B. N.: Les antihistaminiques de synthèse: Essais de chimiothérapie des états allergiques, Arch. internat. de pharmacodyn. et de thérap. **68**: 339, 1942.
25. Bovet, D., Horclois, R., et Walthert, F.: Propriétés antihistaminiques de la N-p-méthoxybenzyl-N-diméthylaminoéthyl a aminopyridine, Compt. rend. Soc. de biol. **138**: 99, 1944.
26. Code, C. F.: A Discussion of Benadryl as an Antihistamine Substance, Proc. Staff Meet. Mayo Clin. **20**: 439, 1945.

27. Ghiselin, A. D., Jr.: The Treatment of Seasonal and Nonseasonal Hyperesthetic Rhinitis With Anthallan, Bull. N. Y. Acad. Med. 22: 320, 1946.
28. Editorial, Anthallan and Hyperesthetic Rhinitis, J. A. M. A. 131: 745, 1946.
29. McGavack, T. H., Elias, H., and Boyd, L. J.: Some Pharmacological and Clinical Experiences With Benadryl, Clinical Research Meeting, June 5, 1946, Bull. New York Acad. Med. 22: 481, 1946.
30. Epstein, S.: Treatment of Allergic Conditions With Pyribenzamine and Benadryl, Wis. Med. J. 45: 489, 1946.
31. Parke, Davis and Company, Medical Division, Unpublished data.
32. Reinstein, H., and McGavack, T. H.: The Nature of Benadryl Activity: Glucose Tolerance Curves, J. Clin. Endocrinol. 6: 643, 1946.
33. Friedlaender, S., and Feinberg, S. M.: Histamine Antagonists. III. The Effect of Oral and Local Use of B-Dimethylaminoethyl Benzhydryl Ether Hydrochloride on the Whealing Due to Histamine, Antigen-Antibody Reactions and Other Whealing Mechanisms, Therapeutic Results in Allergic Manifestations, J. Allergy 17: 129, 1946.
34. McElin, T. W., and Horton, B. T.: Clinical Observations on the Use of Benadryl: A New Antihistamine Substance, Proc. Staff Meet. Mayo Clin. 20: 417-429, 1945.
35. Arbesman, C. E., Koepf, G. F., and Miller, G. E.: Some Antianaphylactic and Antihistaminic Properties of Pyribenzamine, 17: 203, 1946.
36. Eisenberg, Harold J.: Personal communication.
37. Ratner, B., Jackson, H. C., and Gruehl, H. L.: Transmission of Protein Hypersensitiveness From Mother to Offspring. I. Critique of Placental Permeability, J. Immunol. 14: 249, 1927.
38. Loew, E. R., MacMillan, R., and Kaiser, M. E.: The Antihistamine Properties of Benadryl, B-Dimethylaminoethyl Benzhydryl Ether Hydrochloride, J. Pharmacol. & Exper. Therap. 86: 229, 1946.
39. Curry, J. J.: The Effect of Antihistamine Substances and Other Drugs on Histamine Bronchoconstriction in Asthmatic Subjects, J. Clin. Invest. 25: 792, 1946.
40. Feinberg, S. M.: Histamine Antagonists. II. Summary of Developments in Nonspecific Inhibition of Histamine, Anaphylaxis, and Allergy, J. Allergy 17: 217, 1946.
41. Logan, G. B.: The Use of Benadryl in Treating Some of the Allergic Diseases of Childhood, Proc. Staff Meet. Mayo Clin. 20: 436, 1945.
42. Literature from Ciba Pharmaceutical Products.
43. Curtis, A. C., and Owens, B. B.: Beta-Dimethylaminoethyl Benzhydryl Ether Hydrochloride (Benadryl) in Treatment of Urticaria, Arch. Derm. & Syph. 52: 239, 1945.
44. Shaffer, L. W., Carrick, L., and Zackheim, H. S.: Use of Benadryl for Urticaria and Related Dermatoses, a Preliminary Report, Arch. Dermat. & Syph. 52: 243, 1945.
45. Levin, S. J.: B-Dimethylaminoethyl Benzhydryl Ether Hydrochloride (Benadryl), Its Use in Allergic Diseases, J. Allergy 17: 145, 1946.
46. O'Leary, P. A., and Farber, E. M.: Benadryl in the Treatment of Urticaria, Proc. Staff Meet. Mayo Clin. 20: 429, 1945.
47. Eyerman, C. H.: Clinical Experiences With a New Antihistamine Drug, J. Allergy 17: 210, 1946.
48. Todd, L. C.: Urticaria With Observations on the Use of the New Antihistamine Drug, Benadryl, J. South. Med. & Surg. 108: 1, 1946.
49. Barefoot, S. W., Riley, K. A., and Kuhn, B. H.: B-Dimethyl-aminoethyl Benzhydryl Ether Hydrochloride (Benadryl) in the Treatment of Urticaria and Related Dermatoses, N. Carolina M. J. 7: 150, 1946.
50. Feinberg, S. M., and Friedlaender, S.: Relief of Dermographism and Other Urticaries of Histamine Origin by a Synthetic Benzhydryl Alkamine Ether (Benadryl), J. Allergy 16: 296, 1945.
51. Schwartz, E., and Levin, L.: Benzhydryl Ether Hydrochloride (Benadryl) in the Symptomatic Treatment of Allergy, N. Y. State J. M. 46: 1233, 1946.
52. Bowen, R.: Benadryl, Its Therapeutic Value in Allergy, Texas State J. Med. 42: 188, 1946.
53. Koelsche, G. A., Prickman, L. E., and Carryer, H. M.: The Symptomatic Treatment of Bronchial Asthma and Hay Fever With Benadryl, Proc. Staff Meet. Mayo Clin. 20: 432, 1945.
54. Symposium on Antihistaminic and Antianaphylactic Drugs, J. Allergy 17: 129, 142, 145, 151, 203, 210, 1946.
55. Arbesman, C. E., Koepf, G. F., and Lenzner, A. R.: Clinical Studies With Pyribenzamine, J. Allergy 17: 275, 1946.
56. Feinberg, S. M., and Friedlaender, S.: Histamine Antagonists: IV. Pyribenzamine in Symptomatic Treatment of Allergic Diseases, to be published in Am. J. Med. Sc.

57. Friedlaender, S.: Experimental and Clinical Evaluation of Synthetic Antihistaminic Drugs, Am. J. Med. 1: 174, 1946.
58. Williams, H. L.: The Syndrome of Physical or Intrinsic Allergy of the Head. III. Vasomotor Rhinitis and the Vasodilating Pain Syndrome; Their Relationship to Myalgia and Endolymphatic Hydrops (Ménière's disease) and the Reasons for Including All Four as the Syndrome of Physical Allergy of the Head, Proc. Staff Meet. Mayo Clin. 21: 58-64, 1946.
59. Feinberg, S. M.: Allergy in Practice, ed. 2, Chicago, 1946, The Year Book Publishers.
60. Waldbott, G. L.: Clinical Research With Benadryl, J. Allergy 17: 142, 1946.
61. Koelsche, G. A., Prickman, L. E., and Carryer, H. M.: The Symptomatic Treatment of Bronchial Asthma and Hay Fever With B-Dimethylaminoethyl Benzhydryl Ether Hydrochloride, J. Allergy 17: 151, 1946.
62. Hallenbeck, G. A.: Studies on the Effect of Thymoxyethyldiethylamine (929 F) and N-Diethylaminoethyl-N-Ethylaniline on Gastric Secretion in the Dog, Am. J. Physiol. 139: 329, 1943.
63. Koepf, G. F., Arbesman, C. E., and Munafo, C.: Chronic Toxicity of Pyribenzamine, J. Allergy 17: 271, 1946.
64. Slater, B. J., and Francis, N.: Benadryl, a Contributing Cause of an Accident, J. A. M. A. 132: 212, 1946.
65. Geiger, J., Rosenfield, S. Z., and Hartman, D. L.: Unusual Reaction Following Benadryl Administration, J. A. M. A. 133: 392, 1947.
66. Weil, H. R.: Unusual Side Effect From Benadryl, J. A. M. A. 133: 393, 1947.
67. Borman, M. C.: Danger With Benadryl of Self-Medication and Large Dosage, J. A. M. A. 133: 394, 1947.
68. Dale, H. H.: Croonian Lectures. On Some Chemical Factors in Control of Circulation, Lancet 1: 1179, 1233, 1285, 1929.
69. Code, C. F.: The Histamine Content of the Blood of Guinea Pigs and Dogs During Anaphylactic Shock, Am. J. Physiol. 127: 78, 1939.

GENITOURINARY CONDITIONS IN INFANTS AND CHILDREN

HERMAN L. KRETSCHMER, M.D., SC.D.
CHICAGO, ILL.

UROLOGY as a specialty began when Max Nitze paved the way to more precise urologic diagnosis with his invention of the cystoscope. The progress of urology can be divided into the precystoscopic and cystoscopic eras, which enabled one to pass from speculative or theoretical views to one of accurate diagnosis.

The application of the knowledge gained in the development of urology lagged in the field of pediatrics for the following reasons: (1) for the want of small instruments and not because similar conditions were not found in the young; (2) the sentimental objections to the use of the cystoscope and instrumentation in these little patients; (3) the lack of knowledge that complete urologic study was possible in infants and children; (4) the failure of both pediatrician and general practitioner to utilize modern methods of urologic diagnosis; (5) lack of cooperation between pediatrician and urologist, the former treating the child medically or expectantly with the hope that the condition would clear up, the result being that by the time the case reached the urologist, irreparable injury had been done to the upper urinary tract; and (6) the urologist rarely had the first opportunity to examine and study these patients.

In general, many of these statements have undergone great changes. Instead of these patients being seen with far-advanced lesions, they are referred for study at a much earlier time. Unfortunately, some of the above statements still hold true. On the other hand, the keenly alert pediatrician is fully aware of them. For example, some of these patients with so-called pyelitis have been referred to me at as early as 2 months of age.

Urologists, in this country more than any other, have taken a keen interest in the subject of urology in children. Their continuous interest in seeking smaller and better instruments, as well as in diagnosis and treatment, stands in marked contrast to the European urologists, whose efforts have been sporadic.

THE EVOLUTION OF SMALL UROLOGIC INSTRUMENTS

It is extremely interesting to review the development of small urologic instruments and the role played by urologists of this country in their perfection. It is a far cry from Nitze's statement that cystoscopy was not possible in boys under 10 years of age. Age is no longer a contraindication. I have examined a boy 7 days old with a cystoscope.

As early as 1902, Berliner diagnosed a hemangioma of the bladder in a female, 11 years of age, with the cystoscope. In 1908, Portner described a child's observation and catheterizing cystoscope. Bacharach, in 1910, diagnosed

Presented before the Fifteenth Annual Meeting of the American Academy of Pediatrics, Pittsburgh, Pa., Feb. 24-27, 1947.

telangiectasis of the bladder in a girl of 13 years by cystoscopic examination. Casper and Jacoby, in 1911, each described a cystoscope that could be used in children.

To the late Edwin Beer of New York belongs the credit for developing the first practical catheterizing cystoscope to be used on children, which he described in 1911. The youngest girl on whom Beer used cystoscopy was 14 months of age and the youngest boy was 5 years old. The youngest patients whose ureters he catheterized were a girl of 5 years and a boy of 10 years.

In 1924, Butterfield constructed a double catheterizing cystoscope of 16 F. caliber, and in 1930 he described a new baby cystourethroscope for purpose of examination, catheterizing the ureters, and which also permitted the use of the fulgurating current. In 1929, McCarthy presented his miniature cystoscopic outfit. Corbus, in 1930, described a children's observation, irrigating, and catheterizing cystoscope less than 11 F. in caliber. In 1932, Sprenger brought out a single catheterizing cystoscope of 10 F. caliber and Young presented his new double catheterizing cystoscopes for adults and infants. In 1936, Campbell's universal miniature cystoscopic outfit was evolved.

In the discussion of the role played by the urologists of this country in the development of small efficient instruments, great credit must be given to the Wapplers for their untiring energy, ingenuity, and unending enthusiasm for aid and cooperation.

THE GROWING CONSCIOUSNESS OF THE APPLICABILITY OF THESE INSTRUMENTS

In addition to those interested in the development of these small instruments, many others are to be given credit for their readiness to accept and apply the instruments, and to stress repeatedly the value and feasibility of employing them in infants and children.

As early as 1917, Quinby directed attention to cystoscopy and ureteral catheterization in children. From then on there is a steady and continuous stream of contributions by Beer, Bugbee, Campbell, Hinman, Hyman, Kretschmer, Mertz, Schmidt, Stevens, and many others too numerous to mention here, who emphasized that no longer can age be used as an alibi against complete urologic examination in infancy and childhood, as in general the indications and contraindications for cystoscopy in children and adults are identical.

This increasing enlightenment in the realm of pediatric urology has helped to alleviate suffering in the young and prevent much unnecessary invalidism in adult life. Diagnosis is made early, proper treatment is instituted, and better results are obtained.

ANOMALIES OF THE URINARY TRACT

Since the advent of modern urologic diagnosis, and especially since the routine use of intravenous urography, the old idea that congenital anomalies of the urinary tract are rare has been completely disproved. It is surprising how frequently renal anomalies are found.

It is to be emphasized that the mere presence of an anomaly does not indicate surgical intervention unless the anomaly has produced changes; for example, stone, hydronephrosis, and recurring attacks of pyelonephritis. Then, too, it should be borne in mind that the symptoms attributed to the anomaly may be due to some other condition, and operation under these circumstances would fail to relieve the patient of the symptoms.

Abnormalities of the urinary tract assume clinical significance when pathologic processes develop in them. It is believed by some that the anomalous kidney is more likely to be the seat of disease than the normal kidney. The mere presence of an anomaly does not indicate that symptoms will occur because of the anomaly itself. Congenital anomalies of the urinary tract not infrequently produce interference with urinary drainage so that stasis results, and sooner or later infection intervenes and medical management has no effect on the condition.

Helmholtz, many years ago, stated that when pyuria persists longer than four or six weeks despite intensive medical therapy, a complete urologic examination should be carried out. It is interesting to note the frequency with which congenital anomalies are found in patients with persistent pyuria and in patients with relapsing pyelonephritis who fail to respond to efficient medical treatment.

Lowsley and Butterfield, in 1926, reported 100 cases of urologic conditions in children and found twenty-nine congenital anomalies; thirteen of such a nature as to predispose to infection of the urinary tract. In 1928, Mertz reported twenty patients with persistent pyuria in which the basis was congenital anomalies. In 1937, I found that twenty-four of my 101 reported cases of hydronephrosis were associated with congenital anomalies of the kidneys and ureters, and sixteen cases (40%) of hydronephrosis were associated with obstruction at or in front of the bladder neck.

These figures are not to be construed as to the frequency of the occurrence of anomalies, but only to indicate how frequently they are present in patients with chronic pyuria and relapsing pyelonephritis.

It is well known that children, as well as adults, often present themselves with obscure intra-abdominal symptoms, when the symptoms are due to overlooked urologic conditions. It is perfectly obvious that these patients should have the benefit of complete urologic study. My experience in this group of cases coincides with that of Mertz and Hamer. In studying 167 children over a period of five years, they found that the most frequent clinical manifestations of an upper urinary tract anomaly were chronic pyuria with or without fever, abdominal colic, and abdominal tumor.

Bilateral Renal Agenesis is of no clinical interest because the condition is incompatible with life.

Supernumerary Kidney.—True supernumerary kidney is among the rarest of all renal anomalies. I reported a case in 1915 and another in 1929 together with a review of twenty-nine cases from the literature. The largest number of supernumerary kidneys occurred in the second decade of life. The only reported

case of this anomaly in a child was reported by Pick (quoted by Neckarsulmer), as found at autopsy in a girl, aged 9 months. A recent paper by Carlson states that only forty-six cases of supernumerary kidney have been found up to 1946.

Because of its great rarity and because it is discovered in the adult, it has little interest for the pediatrician. Unfortunately, many cases of double kidney pelvis have been reported as supernumerary kidney. This is careless medical speech. Some patients have been told they had three kidneys because they had a double kidney.

Simple Renal Ectopia or Dystopia.—Although the number of cases reported in adults increases from year to year, the number found in children is very small. I have never seen a child with this condition who had symptoms and required treatment. It seems to be fair to assume that this congenital anomaly does not begin to produce symptoms until adult life. However, the possibility of its occurring in children should be borne in mind. Its presence is readily demonstrable by urologic examination.

Solitary Kidney may be recognized at any age. The symptoms of a diseased solitary kidney are no different than when two kidneys are present. Symptoms may be pain, hematuria, pyuria, or anuria, and it is important to utilize all modern diagnostic methods so that the solitary kidney can be recognized and conservative surgery employed and not err in removing the solitary kidney.

Because only one kidney can be demonstrated by intravenous urography, one must not assume that we are dealing with a case of solitary kidney. A 5-year-old boy referred to me with a diagnosis of solitary kidney made from the intravenous urogram, showed on retrograde pyelogram a small, congenital, hypoplastic kidney without function which had no visualization in the intravenous urogram.

Horseshoe Kidney or Fused Kidney.—I have seen but one child with fused kidney. This condition can be readily recognized in the plain roentgen film and in the pyelogram. It is important because of its susceptibility to infection and stone formation, due to its anomalous position, the anomalous blood supply, and the course of the ureters, all of which interfere with drainage.

Although a great many articles dealing with this subject are found, few deal with children. Some of the earlier American reported cases of horseshoe kidney in children are: Hand's two cases in 1898; Caverly's report in 1904; Eisendrath's case in 1912; and Thompson's case in 1913. Bugbee and Wollstein, in 1924, in 4,903 autopsies in children, found three cases of fused kidney. In Campbell's series of 12,080 pediatric autopsies, the incidence was 1:335. He found this anomaly twice in over 700 children subjected to pyelography and in one of these cases the condition was recognized only at operation. Mertz and Hamer, in 1938, discovered three instances in 167 patients.

It appears that this lesion does not become the seat of disease very frequently in children.

Unilateral fused kidney with ureteral reduplication is rare. Up to 1941, only six cases had been reported; three of these occurred in children and were reported by Wilcox in 1921, Hess in 1923, and Bugbee in 1924.

Renal Hypoplasia results from congenital failure of development, and is often associated with other abnormalities. There is comparatively little written on the subject. The clinical importance of this anomaly is that the small amount of renal tissue present, when bilateral, is not sufficient to sustain life. The hypoplastic kidney is more subject to infection than a normal kidney. This condition has been frequently associated with hypertension, and urologists many years ago recognized that when the hypoplastic kidney was removed, the hypertension disappeared, and the blood pressure returned to normal or nearly normal.

In 1942, Powers and Murray reported on a boy, aged 6, who had hypertension associated with aplasia of one kidney, which was relieved by nephrectomy. Their survey of the literature disclosed fourteen American cases in whom juvenile hypertension was associated with unilateral renal disease which was relieved by removal of the affected kidney. Higbee, in 1944, reported an interesting case of a child aged 12, who had a congenital renal hypoplasia associated with hypertension.

E. S., aged 4, was admitted to the Presbyterian Hospital Sept. 14, 1946, and discharged Sept. 22, 1946.

The patient had had many attacks of fever associated with pus in the urine. Two months before admission to the hospital, his mother discovered gross blood in the urine. Large clots were passed with the urine. The hematuria continued for two days. Following this attack of hematuria, the child developed frequency of urination and dysuria. At this time he had a temperature of 103° F. The temperature gradually came down and was normal at the end of two weeks.

Physical examination of head, eyes, ears, and nose was negative. Examination of throat showed slight enlargement of tonsils. Heart, lungs, abdomen, and external genitalia were negative. Central nervous system was negative. Blood pressure was 118/78. Examination of blood on Sept. 15, 1946, showed hemoglobin, 12 Gm.; red blood corpuscles, 4,790,000; white blood corpuscles 15,400. Examination of urine showed albumin, sugar, casts negative; one or two red blood corpuscles to the high power field; no pus cells. Nonprotein nitrogen was 45 mg. per cent; albumin globulin was 1.53; total protein was 8.22. X-ray was negative for stone. Intravenous pyelogram showed right kidney to be normal; there was no visualization on the left side. Cystoscopic examination was made elsewhere; the bladder was normal. Retrograde pyelogram was made on the left side. The pyelogram was compatible with and typical of a hypoplastic kidney.

Operation was done Sept. 16, 1946, with ether anesthetic. Left nephrectomy was done by H. L. K. The patient made an uneventful recovery and left the hospital on the sixth day.

Pathologic report by Dr. George M. Hass gave a diagnosis of: congenital malformation of left kidney; congenital hypoplasia of left kidney; and slight, chronic pyelonephritis.

Double Kidney and Double Ureter.—Formerly considered very rare in both children and adults, the routine use of intravenous urography has demonstrated that they occur quite frequently and are often found without their presence being suspected. Here again, it would be well to emphasize the fact that the mere presence of this anomaly is no indication for operation. On the other hand, in patients with chronic pyuria, hydronephrotic changes in one half of the double kidney, and recurring attacks of pyelonephritis, nothing short of heminephrectomy will effect a cure.

The condition may be unilateral or bilateral and may be associated with reduplication of the ureter. Ureteral reduplication may be unilateral or bilateral, complete or incomplete. The two ureters may fuse anywhere from just below the renal pelvis to just outside the bladder. Where the two ureters fuse outside the bladder, there are two ureteral orifices in the bladder. This is the more common type of reduplication. Where the reduplication is complete, there are, if unilateral, three ureteral orifices in the bladder, and, if bilateral, four.

Fig. 1.—Congenital hypoplasia of the kidney with chronic pyelonephritis.

As a rule, the upper half of the double kidney is the one harboring the pathologic lesion. I have seen only one patient in whom the lower half of the double kidney was the seat of extensive hydronephrotic atrophy. Fortunately for these children, the upper or rudimentary half is diseased, which makes its removal simple, and one is able to save the lower and, incidentally, the larger half.

The operation of heminephrectomy is a simple one, and the results are most spectacular.

Polycystic Kidney.—Polycystic renal disease is often hereditary and is characterized by the formation of cysts within the parenchyma, which results in the surface of the kidney being studded with small cysts. The exact incidence of this disease is unknown, as statistics of various authors differ considerably. There are not too many reported cases of this condition in children, which is probably due to the fact that many times the condition is not recognized during life, and clinical manifestations in the majority of patients with this disease do not appear until adulthood.

I have seen two cases of polycystic disease in children. In one, the kidneys were normal in size and had not yet reached the typical cyst formation, so that the surface of the kidneys was smooth. In the second, the kidneys were enormously enlarged and many cysts were found. This case is to be reported in detail at a later date.

Campbell has seen forty-eight cases in children at necropsy. Yardumian and Ackerman, in 1943, reviewed ten cases of congenital polycystic kidney from the Montefiore Hospital; one of these concerned a newborn infant. H. C. Shands, in 1945, reported three infants who had simultaneous occurrence of polycystic kidneys and erythroblastosis fetalis. Roos, in 1941, reported a bilateral polycystic kidney in a girl of 5 months. In 1945, Smith and Graham published a case of a child, 8 years old, with congenital medullary cysts of the kidneys with severe refractory anemia. No other members of the family were known to have had polycystic kidneys.

Solitary Cysts of the Kidney are rare in children. Chalkley and Sutton, Jr., in 1943, published a personal case of an infected solitary cyst of the kidney in an 11-year-old child. In their review of the literature, they were only able to gather ten cases of solitary renal cysts in children.

Braasch and Hendrick, in 1944, reported that simple renal cysts were observed in only four patients under 21 years of age, two of whom were infants, 8 and 15 months old.

Ectopic Ureteral Orifice.—Closely associated with the subject of ureteral reduplication is the abnormal insertion of one of the ureteral orifices outside the bladder. In the female, the ectopic orifice may be located in the urethra, generally on the floor. It may be located to one side of the external urethral orifice or below it, in the vagina, or in the uterus. In the male, the ectopic opening has been found in the prostatic urethra, the prostate itself, in the seminal vesicle, or in the vas deferens.

It occurs more frequently in the female than in the male, and is often overlooked for many years. All but one of the cases of ectopic ureter that I have seen have been cases of double ureter. The one exception occurred in a woman, aged 21, in whom both ureters terminated in the urethra (reported with Heaney in 1929).

As a rule the ectopic ureter drains the upper half of a double kidney. As a result of this anomaly this half of the kidney undergoes hydronephrotic atrophy and frequently is infected.

A tentative diagnosis can almost always be made from the history. A careful history will elicit the fact that the patient is "wet all of the time," losing urine continually, day and night, irrespective of the act of micturition. This fact should at once arouse suspicion of the presence of an ectopic ureter. Unfortunately, this condition is all too frequently diagnosed as enuresis.

Some patients have had many cystoscopic examinations, including several sets of retrograde and intravenous pyelograms, and have had all sorts of treatments for many years without any influence on the symptoms, due to the fact that the cause of the symptoms was not recognized.

The diagnosis is made by finding the ectopic ureteral orifice, which can readily be located in girls with a good exposure, proper light, and a discerning eye. The intravenous urogram is often helpful. It shows the presence of a double pelvis and two ureters. If the upper half of the double kidney has undergone hydronephrotic atrophy, there is no visualization of the upper half. However, the configuration of the urogram is most suggestive.

The treatment is heminephrectomy.

L. S., a single woman teacher, aged 27, consulted me on June 18, 1935.

The previous history is irrelevant. The patient has had many urologic examinations and treatment without relief of her complaint. Her present complaint was inability to hold her urine. She stated she had incontinence as long as she could remember, and had been obliged to wear a napkin night and day because of her condition. She had no burning, urgency, hematuria, pain, or frequency. She stated that she voided normally.

On the floor of the urethra just behind the external urethral orifice was seen an opening from which urine was emitted. A ureteral catheter was passed into this opening and a retrograde pyelogram was made.

Cystoscopic examination June 24 showed the bladder and ureteral orifices to be normal. Retrograde pyelograms were normal. The pyelogram made with a catheter in the aberrant orifice showed a great deal of dilatation of the calyces and dilatation of the ureters. Examination of the urine was negative. The urine was sterile on culture.

Blood count, blood pressure, and blood chemistry were normal.

A diagnosis of double kidney with complete reduplication of ureter, one of which was ectopic with hydronephrotic atrophy of the upper half of the double kidney was made, and operation was advised.

Operation was done June 26 with ethylene anesthesia. It was a right heminephrectomy. The upper embryonic half of the kidney was small. It was soft, due to hydronephrotic atrophy. The embryonic half had its own blood supply. The patient made a smooth and uneventful convalescence and was discharged July 13, 1935.

Ureterocele.—This condition is sometimes called cystic dilatation of the lower end of the ureter. Although it is relatively uncommon, it occurs frequently enough to bear its possibility in mind. This lesion is important because of its devastating effect on the kidney.

According to Hinman it is of two types: (1) a ballooning out of the vesicoureteral mucosa because of a narrow, constricted ureteral meatus and (2) herniation of all the layers of the ureteral wall into the bladder.

Because of the interference with drainage, hydronephrosis is always present. When infection is superimposed, the patients have chills and fever with a marked pyuria. As a result, a diagnosis of pyelitis is made, and the patient is given medical treatment for long periods of time, to no avail.

The ureterocele may be unilateral or bilateral, and may vary greatly in size. In some cases the ureterocele protrudes from the external urethral orifice.

The diagnosis is readily made upon cystoscopic examination which shows a rounded, semitranslucent swelling covered with smooth pink mucous membrane. When the ureterocele is large it may produce obstruction to urination, thus resulting in hydronephrosis. A characteristic picture is obtained in the cystogram obtained with intravenous urography. This shows the presence of a large filling defect in the cystogram (Fig. 3).

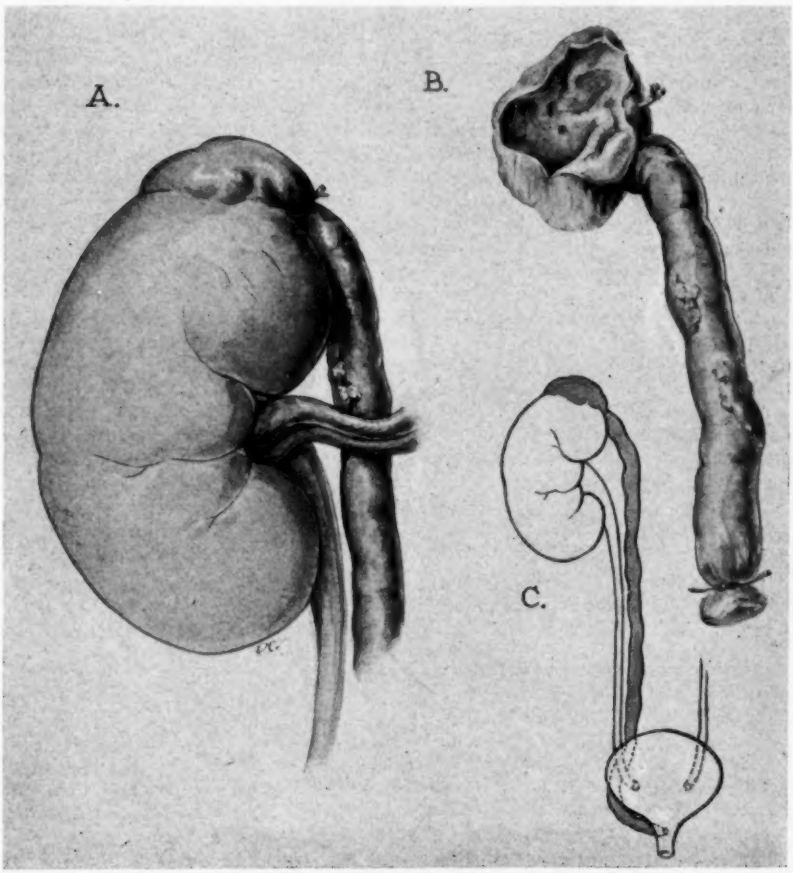


Fig. 2.—*A*, Double kidney and ureter; *B*, almost complete hydronephrotic atrophy of the rudimentary upper half of the kidney; *C*, termination of the aberrant ureter in the urethra.

A ureterocele may be found at the end of a single ureter and if the condition goes unrecognized for a long time the changes in the kidney may be so far advanced that nephrectomy may be necessary. When the ureterocele occurs at the end of a reduplicated ureter, heminephrectomy may be indicated. The

ureterocele is best and easiest treated with the high frequency spark or by resection with the resectoscope. In all of the children I have seen the condition fortunately was found at the end of an accessory or double ureter, so that only the upper half of the double kidney had undergone hydronephrotic atrophy with severe secondary infection. Heminephrectomy resulted in a complete cure.

N. L., aged 20 months, was admitted to Presbyterian Hospital Sept. 23, 1945.

The mother stated that since birth it had been apparent to her that the child had pain on urination. The child held her urine as long as possible and screamed while passing urine.

Examination of the urine prior to admission to the hospital showed pus and albumin on several occasions. The child was referred for diagnosis and treatment.

Physical examination was completely negative. Blood examination was normal. Examination of the urine showed acid: albumin 1+; casts, none; and many leucocytes. Blood chemistry on Sept. 25, 1945, showed urea nitrogen 12 mg. per cent; uric acid 3.2 mg. per cent; creatinine 1.3 mg. per cent; nonprotein nitrogen 38 mg. per cent. There were 12,800 leucocytes per cubic millimeter. Culture showed a luxuriant growth of *Escherii coli communis*.

Roentgen ray examination September 24 showed no stone shadow. Right pyelogram showed dilatation of pelvis, calyces, and ureter. Pyelogram on left side showed an enlarged kidney; pelvis and calyces were normal. A large, round, filling defect was seen on the base of the bladder (Fig. 3). Cystoscopic examination showed the presence of a large, smooth, round swelling covered with mucous membrane. Because of the large size of this swelling, it was impossible to locate the ureteral orifices. Diagnosis of cystic dilatation of the vesical end of the ureter was made. Bipolar fulguration was carried out on September 25.

A second pyelogram on Oct. 1, 1945, was made before the child was discharged from the hospital. The previously seen dilatation of the right ureter returned to normal in this short period of time, six days after fulguration. Because of the large outline of the kidney on the left side, a tentative diagnosis of double kidney with no visualization of the upper half was made. Because of the dilatation of the right ureter, the impression was gained that the cystic dilatation of the ureter was right sided. Subsequent events proved that the cystic dilatation took its origin from the left side. It is interesting, therefore, to note that although the cystic dilatation was left sided in origin, it resulted in a hydroureter on the right side.

The patient was brought back to the hospital for cystoscopic examination Nov. 24, 1945. Ethylene anesthesia was used. The child strained a great deal and a large mass of tissue protruded from the external ureteral orifice. This had the appearance of the cyst which was fulgurated previously. It was grasped with an artery forceps and pulled out as far as possible and cut off with the fulgurating current.

The mother was instructed to bring the child back for further observation and the child was admitted again to the Presbyterian Hospital on Sept. 17, 1946.

Physical examination was negative. Blood count was normal. Examination of urine: cloudy; albumin; many pus cells; many bacteria; leucocytes, 18,000 pus cells per cubic millimeter.

Cystoscopic examination on Sept. 18, 1946, showed the right ureteral orifice to be normal. On the left side were seen two ureteral orifices; one was normal, the other was dilated. Both left ureters were catheterized and a set of retrograde pyelograms were made with the following report (Fig. 4): double kidney with double ureter; and hydronephrotic atrophy of the upper half. Operation was advised.

Heminephrectomy was on September 18, with ethyl chloride anesthesia. The ureter from the lower or large half was normal. The ureter from upper or embryonic half was very much enlarged and its walls were thick. The lumen and pelvis were dilated. There was almost complete hydronephrotic atrophy (Fig. 5). The child had a smooth and uneventful convalescence and was discharged Sept. 27, 1946.

Congenital Stricture of the Ureter.—In some cases of large hydronephroses, especially early in life, a diagnosis of congenital stricture of the ureter at the

Fig. 3.—Large filling defect in the cystogram due to the uterocele.

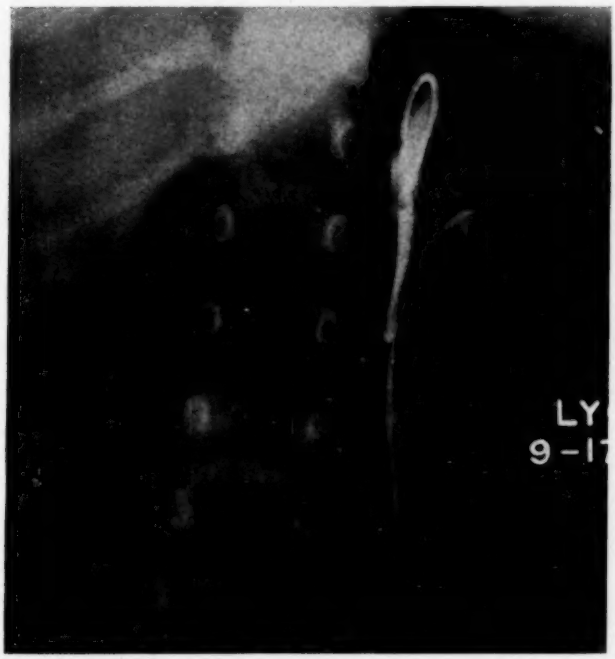


Fig. 4.—Retrograde pyelogram. Double kidney with hydronephrotic atrophy of the upper rudimentary half.

ureterovesical junction is made. As a rule there is no change in the ureteral orifice itself and no obstruction to the passage of the ureteral catheter.

Unfortunately, the relationship of bladder neck obstruction and the so-called stricture of the ureter is not recognized and these patients are subjected to long courses of ureteral dilatation without obtaining the desired results. Careful study of these patients has shown that in the majority the primary lesion was not at the ureterovesical junction, but at the neck of the bladder, producing obstruction to urination with hypertrophy of the bladder wall and resulting compression of the ureter in its intramural part. Therefore the treatment should be directed to the obstruction at the bladder neck.

Bladder Diverticulum.—Practically all cases of vesical diverticula are congenital and secondary to obstruction at or in front of the bladder neck with the exception of those due to organic disease of the central nervous system. These facts must be borne in mind in the treatment.

There are no symptoms from which a diagnosis can be made and the diverticulum is generally discovered during a routine urologic examination. An intravenous urogram will often disclose vesical diverticula when least suspected. This occurs in both adults and children. Cystoscopic examination often reveals a diverticulum and determines its exact location. However, in the presence of a severe cystitis the opening is easily overlooked.

In 1934, I found nineteen authentic cases of diverticula of the bladder in infants and children in the literature and added two clinical cases and four found at autopsy. The condition is frequently overlooked in children because of the absence of a typical symptom complex. In the six cases reported in my paper, the following symptoms were noted: suprapubic tumor in five; pyuria in three; painful urination, two; chills and fever, vomiting, one; dribbling, one; restlessness, fever, diarrhea, and loss of weight (no urinary symptoms), one; retention, one; difficult urination, one; albuminuria, one; and edema of the left leg, one.

The treatment is directed toward the removal of the obstruction. If the diverticula are small, nothing further than the relief of the obstruction is indicated. However, in large diverticula, especially when they do not empty and infection persists, diverticulectomy is necessary.

Exstrophy of the Bladder.—We owe much to the relentless efforts of Coffey, Higgins, Lower, Hinman, Walters, Ladd, and many others who urged early transplantation of the ureters into the bowel. Although Simon first published his technique in 1852 and many authors have described various operations for transplanting the ureters into the intestinal tract, the great stimulus to the treatment of these patients was given by Coffey in 1911. He subsequently modified his original technique and many other authors have presented their various techniques, all of which resulted in a renewed interest in this subject and in the possibility of surgical relief of an intolerable condition.

There is no difference of opinion today on the subject of treatment. Some variances of opinion still exist as to the age when surgery should be undertaken. The general rule was to wait until the child was 3 years of age, so that

control of the bowel function was well established. Higgins in recent years has changed his attitude in that he has seen children of 3 who have already impaired renal function with hydronephrosis and dilatation of the ureters. The determining factor in deciding on operative intervention is the competency of the rectal sphincter in the individual case and before infection has been introduced into the kidneys, and Higgins believes that the operation can be performed any time after the age of 3 months. My preference is to wait until the child is 18 months or 2 years old, and to transplant one ureter at a time. There is increased danger when both ureters are transplanted at once.

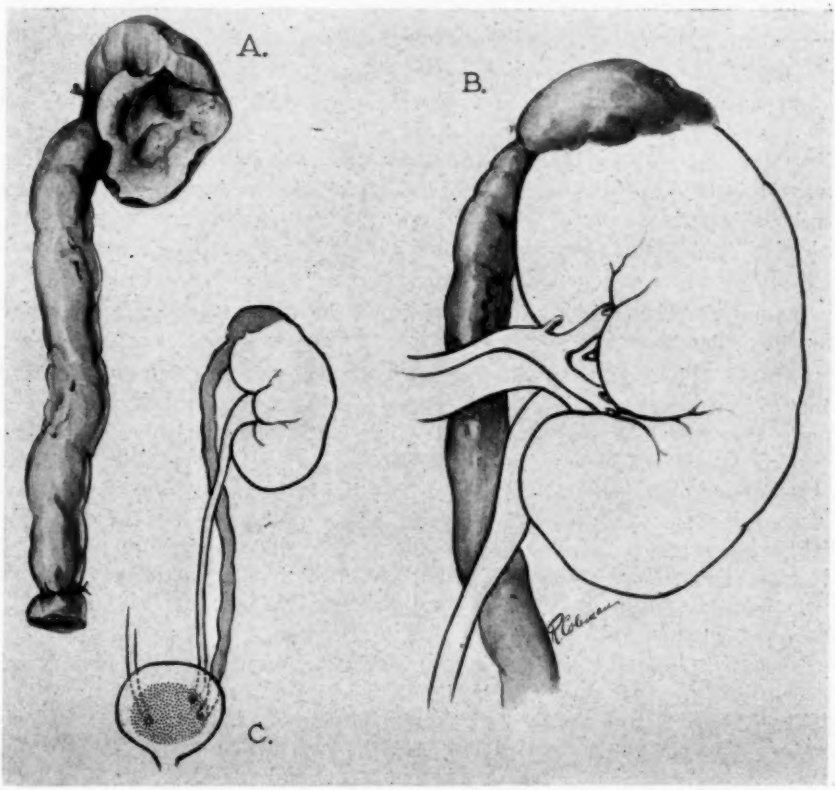


Fig. 5.—*A*, Marked dilatation of the ureter and hydronephrotic atrophy of rudimentary half; *B*, crossing of the ureters; *C*, dotted area illustrates size of uterocele covering opposite ureter.

Obstructions at the Vesical Neck.—With advances being made in diagnostic urology, many abnormalities which heretofore were not diagnosed clinically are now recognized with more frequency. Obstructive lesions at the vesical neck may be of either mechanical or neurologic origin. The causes may be located at the bladder neck or in front of it and may be classified as follows:

(1) contractures at the internal ureteral orifice; (2) median bars; (3) valves in the prostatic urethra; (4) hypertrophy of the verumontanum; (5) lesions of the central nervous system; (6) lesions of the prostate; and (7) extravesical lesions.

Many physicians are still unfamiliar with this pathologic entity and many cases are diagnosed and treated as cases of enuresis.

Of the greatest importance for these children is early diagnosis before irreversible changes occur in the upper urinary tract. The diagnosis of obstruction can be made from the history and the physical examination. The diagnosis of the type of obstruction requires cystoscopic and urethroscopic examination. The use of intravenous urograms and studies of blood chemistry are done in each case.

Our attention should be aroused to the possibility of obstruction by the history of straining, a small weak stream, the fact that it takes the patient a long time to empty the bladder, dribbling during the act of micturition, which may be interrupted once or twice, dribbling between urinations, recurring attacks of infection, and pus in the urine. If, with this group of symptoms, the physical examination shows a suprapubic tumor, the diagnosis of obstruction is complete. There only remains to be determined the cause of the obstruction.

Once the diagnosis has been established the treatment should be carried out immediately.

In 1937, I reported on 101 cases of hydronephrosis in children and found that sixteen were associated with obstruction at or in front of the bladder neck; nine of which were congenital valves, three were stricture of urethra, two were bars, and two were contracted bladder neck. Caulk, in 1936, presented twenty-six cases of urinary obstruction in infants and children which were due to: contractures of the neck in nine; valves in twelve; valve and lobule in one; valve and bar in one; villous mass and valve in one; and lobules in two. Other large series of obstructions at the bladder neck have been reported by Campbell (1937), Mertz and Hamer (1938), Pace (1940 and 1944), and Thompson in 1942.

Contractures of vesical neck may be due to a muscular hypertrophy or a fibrosis of the vesical neck. If urinary difficulty exists from birth, the possibility of a contracted vesical neck should be considered. A complete urologic examination should be carried out and the obstruction removed, either by transurethral resection or suprapubic cystostomy and resection.

The exact incidence of congenital contracture of bladder outlet in childhood is difficult to determine. Many cases are overlooked in childhood until serious symptoms of urinary obstruction appear, and if untreated, the patient dies without the true condition being recognized. Probably this condition occurs more frequently than is apparent, owing to the fact that cases are not reported. Campbell, in 1937, wrote that he had forty-one cases of congenital contracture of bladder outlet in children, and that in a perusal of the literature from 1915 to 1930 he was able to find only twelve cases reported. In 1939, Hendrick-

son and Simon described three cases in children and stated that congenital contracture of the vesical neck is most commonly due to hypertrophy of the musculature of the internal sphincter.

Extravesical Lesions.—Grant, in 1938, reported two cases of tumor arising at the sphincteric margin and acting as ball valves. Retroperitoneal lesions, such as tumors, both benign and malignant, occasionally produce urinary symptoms. As the tumor increases in size, it produces obstruction with resulting hydronephrosis. As the tumor continues to increase in size, lateral displacement of one or both ureters results. Lateral displacement of a ureter in the presence of an abdominal mass is almost always pathognomonic of a retroperitoneal tumor. Although these cases are rare, they do occur occasionally, so that one should bear them in mind in any differential diagnostic problem.

Congenital Valves of the Posterior Urethra.—Although this interesting pathologic entity was first recognized by the Europeans from studies in the post-mortem room, it remained for the urologists of this country to emphasize the fact that congenital valve obstructions of the posterior urethra were of extreme clinical importance, and diagnosis relatively simple. If not relieved, the effects upon the upper urinary tract are devastating and irreversible.

Valvular obstruction of the posterior urethra is congenital in origin, the embryologic reason being unknown. Langenbeck, in 1802, was the first to give an autopsy description, and subsequent reports that appeared were those of Europeans. Tomatschew, in 1870, was the first to regard congenital valves of the posterior urethra as a definite clinical entity.

Knox and Sprunt, in 1912, were the first Americans to recognize and report a case at autopsy in a child 5 years of age. Autopsy showed bilateral hydronephrosis and hydroureters due to valvular obstruction just below the verumontanum. Hugh Young, in 1912, made the clinical diagnosis of congenital valvular obstruction in the posterior urethra, which was confirmed at autopsy in a boy 17 years of age. In 1913, Young operated successfully through a suprapubic incision in a 20-month-old infant. Young, Frontz, and Baldwin, in 1919, reviewed the Johns Hopkins Hospital records, reported twelve cases, presented an exhaustive review of the literature, and found twenty-four authenticated cases of congenital obstruction of the posterior urethra. In 1920, Young constructed a small "baby punch" which was used on a child of seven with congenital valves of the posterior urethra.

The American literature on this interesting condition has been augmented steadily with further reports which indicate that the condition is not uncommon: Randall (1921); Martinson and Reuben (1923); Randall (1923); Day and Vivian (1923); Hausmann (1924); Beer (1924); Ehrich (1925); Hinman's and Kutzmann's excellent review of the literature in 1925, wherein they reported fifty cases of valvular obstruction in the posterior urethra taken from the literature and to this added six personal cases; Hepler, Poynton, and Sheldon (1927); Kretschmer and Pierson (1929); Young and McKay (1929); Hess and Peters (1932); and Lowsley and Kirwin (1934).

Congenital valves may be destroyed by the fulgurating electrode or the resectoscope. For the relief of bars and contractures, transurethral resection by means of the resectoscope is to be done. Before the development of small punches and resectoscopes, suprapubic operation was the method of choice. Some favored attempts to destroy the valves by using a urethral sound. It is my view that this kind of procedure should give way to transurethral resection.

Unfortunately, the diagnosis is not made early, and although the obstruction has been completely removed, changes in the upper tract are irreversible as illustrated in the following case:

D. O'B., aged 8, male, was admitted to Presbyterian Hospital Nov. 17, 1936. The parents recalled that he has had dribbling of urine since infancy. They agreed with the family physician that this was a behavior and not a medical problem. Three months before his admission to the hospital, pus was found in the urine. He was given a thorough medical regime, but the pyuria persisted. At this time he was sent to another hospital for observation and it was discovered that he did not empty his bladder. Roentgen-ray examination showed enormously dilated ureters, kidney pelves, and calyces. At this time the observation was made that after the patient voided, a large amount of urine could still be expressed by suprapubic pressure. The patient also complained of a slight, dull, aching pain in both lumbar areas.

Physical examination showed the patient to be well nourished and not appearing acutely ill. Head and neck, eyes, ears, nose, throat, heart, and lungs were negative. Examination of the abdomen showed a rounded swelling that extended from the symphysis pubis nearly to the umbilicus.

Examination of the urine: sugar negative; albumin a trace; many pus cells. Cell count showed 4,600 white blood cells per cubic millimeter and the culture showed a pure culture of *Bacillus coli*.

Neurologic examination was negative.

Blood chemistry, November 18, showed urea nitrogen 16.8 mg. per cent; creatinine 1.5 mg. per cent; nonprotein nitrogen 42.1 mg. per cent; phenolsulfonephthalein test appearance time twenty minutes output for two hours 40 per cent.

Cystogram on November 18 showed the bladder outline smooth. There was a reflux into both ureters. Both ureters were markedly dilated, the left being larger than the right. Both kidney pelves were markedly dilated and the calyces were clubbed. The kidney pelves and calyces almost filled the entire kidney.

Cystoscopic examination of November 20 showed the ureteral orifices dilated. There was marked trabeculation of the bladder. The internal urethral orifice was edematous, and there was no median bar. The cystoscope was withdrawn into the prostatic urethra and showed the presence of valves. Following the cystoscopic examination, the patient developed complete retention and 800 c.c. of cloudy urine was withdrawn. The catheter was anchored in place and the patient was treated with an indwelling catheter. Jan. 5, 1937, fulguration of valves by means of Bugbee fulgurating electrode was done. The patient was discharged from the hospital January 10. At this time there were two ounces of residual urine.

The patient was readmitted to Presbyterian Hospital April 8, 1946. He wanted to enlist in the Navy and was turned down because of urinary findings. Examination showed no suprapubic tumor. Urine showed albumin 2+; no sugar; and an occasional red blood cell. Culture showed *Bacillus coli*. Residual urine was 1 oz., blood pressure was 110/70, red blood corpuscles 4,720,000, white blood corpuscles 5,300, and hemoglobin 13.8 Gm.

Cystoscopic examination showed marked trabeculation of the bladder. Both ureteral orifices were wide open. There was marked cystitis; urine was pale.

Retrograde pyelograms showed enormous dilatation of ureters, kidney pelves, and calyces. In spite of the fact that the obstruction was removed, there was no change in the dilatation

of the upper urinary tract. It was assumed that the small amount of residual urine (2 oz.) did not result from the persistence of obstruction but apparently was urine that trickled down into his bladder from his enormously dilated kidney, pelves, and ureters.

This case illustrates very graphically the need for early diagnosis and treatment in urinary obstruction.

Hypertrophy of the Verumontanum.—Obstruction to the outflow of urine may be produced by hypertrophy of the verumontanum, and although it is not as frequent as valvular obstruction, contracture, or bars, it is often undiagnosed, as so many of the cases have been autopsy findings. Usually those cases found were associated with bilateral hydronephrosis and hydroureter. In 1910, Swinburne first called attention to enlargement of the verumontanum as a cause of urinary obstruction. In 1923, Bugbee and Wollstein described a case in a child, 3½ years old; in reviewing the autopsy records of Babies' Hospital they found seven patients with enlarged verumontanum causing obstruction of the prostatic urethra.

Lesions of the Central Nervous System.—The common cause of neurogenic bladder disturbance in children is spina bifida, which is usually recognized in the plain roentgen film and should never create any diagnostic problem.

Spinal cord bladder is not a common disease in children. However, the urologist should bear in mind its possibility when the urinary symptoms are prominent and urologic examination does not reveal the cause; then he should suspect some disease process of the central nervous system.

In 1931, I reported three cases in which lesions of the central nervous system produced urinary symptoms. One case was in a female, aged 5½, who had a spinal cord bladder due to poliomyelitis; the second was a malignant tumor of spinal cord with complete retention of urine occurred in a male, 8 years old; and the third was a glioma of the optic chiasm in a girl of 11 years.

Lesions of the Prostate.—Among rare instances of urinary obstruction in children is to be mentioned sarcoma of the prostate. McKay, in 1940, reported two cases and Powell, in 1945, in perusing the records of the Montreal General Hospital for thirty-five years, had two cases of sarcoma of the prostate causing vesical neck obstruction.

Undescended Testicle.—An undescended testicle is generally discovered during a routine physical examination by the pediatrician. The testis may be found at or above the external ring, in the inguinal canal, or in the abdominal cavity. The condition may be unilateral or bilateral.

Great care must be exercised in making this diagnosis. Patients in whom one or both testes were in the scrotum have been referred to me for operation. During the examination, both testes retracted to the external ring, and the scrotum was empty. It is imperative that one must differentiate between a true undescended testicle and a highly retractile testicle.

The diagnosis of an undescended testicle is made when one or both of the testes remain continuously above the external ring, and when the testes do not enter the scrotum. Many theories are given as to the cause of nondescent of the testes. Embryologists maintain that the descent of the testicle is due to

contraction or atrophy of the gubernaculum testis. However, contradictory evidence has been presented by others. Burdoch demonstrated that testicular descent in a normal child occurs before the gubernacular muscle fibers are in evidence. Recently, the causation of cryptorchidism has been attributed to a disturbance of the endocrine glands.

It is to be remembered that many of these undescended testicles do descend spontaneously at or near puberty. Studies have been made which showed that after puberty the undescended testicle does undergo atrophy or remains atrophic. It is claimed by some that the undescended testis is more liable to torsion, trauma, and malignancy. In a large number of cases of undescended testicles there is an associated hernia.

There is still a great deal of difference of opinion in regard to the management of undescended testis. These opinions fall into four groups: (1) that one should wait until puberty before instituting treatment because some of these undescended testes do descend spontaneously at or near puberty; (2) that the patient should be treated with hormones once the diagnosis of undescended testes is made; (3) that the patient should be operated upon just as soon as the diagnosis is made; (4) that the patient should be given a course of hormone treatments and, if the testicles fail to descend, the patient should be operated upon. Those authors holding this opinion believe that the hormone injections make the operation somewhat easier.

One can find sufficient data in the literature to support whatever view he might have on endocrine therapy, despite the various controversial opinions presented.

It should be remembered that there always exists the possibility in the patients who respond to hormone therapy that the testis may have come down without hormones at the time of puberty.

In many patients who have had long courses of hormones, mechanical conditions were the cause for the maldescent—conditions which no amount of hormones could have cured. I believe that true undescended and ectopic testes always require surgical treatment, and do not use hormones before operation. Certainly the hormones have no place in the treatment of retractile testes.

The indiscriminate and long-continued use of hormones is most unfortunate. The stimulating effect of hormones on the growth of the penis and the development of pubic hair in a boy of 10 years or under is most unfortunate. On the other hand, a short course of this treatment for a period of about six weeks, should arouse no objections.

Of interest is the report by Eisenstaedt (1940), who reported marked evidence of degeneration after the use of hormones in a series of patients operated upon. Thompson and Heckel, in 1941, reported successful results in only 27 per cent of their cases. Cone, in 1944, stated, "Our own observations and those of many others have convinced us that artificial stimulation of the retained testis by any gonadotropic or androgenic substances has a small field of usefulness—is practically unnecessary and may be harmful. We must remember that the intimate relationship of the testicle with the thyroid, pituitary, and

adrenal is as yet poorly understood; and it is our belief that stimulation of the endocrine system has harmful potentialities and should be avoided, in that it may result in glandular imbalance or other systemic disturbances." I am in complete accord with the statements of Cone.

SURGICAL TUBERCULOSIS OF KIDNEY

Renal tuberculosis in children is of two types: (1) renal involvement as a part of a generalized miliary tuberculosis and, as such with no surgical interest; (2) surgical renal tuberculosis. It is the latter type of lesion that can be cured when the process is limited to one kidney, and when the diagnosis is made early, the prognosis is excellent.

Cases of renal tuberculosis heretofore were rarely observed clinically because (1) localizing symptoms of renal tuberculosis in children are often absent; (2) the general incidence of tuberculosis in this country has been on the decline, which of necessity means less genitourinary tuberculosis; and (3) failure to subject cases of chronic pyuria to modern methods of urologic diagnosis.

With the increased use of diagnostic urologic methods in children, more patients with chronic renal tuberculosis are being recognized and hence are properly treated. With the more frequent use of complete urologic examination in young patients with so-called chronic pyelitis or cystitis, the true incidence of renal tuberculosis will be found to be much higher than the present collected data indicate except in so far as the incidence of general tuberculosis is on the decline.

The consensus of opinion is that surgical renal tuberculosis is comparatively rare in infancy and childhood. Mathe, in 1936, reviewed the various reports given in the literature, including his own personal cases, comprising in all, 4,698 cases of unilateral surgical renal tuberculosis, and found that 565 (12 per cent) occurred in the young from 1 to 20 years. He does not think that renal tuberculosis is rare in children, but that it has often been overlooked in the child.

On the other hand, the rarity of urinary tuberculosis in children is evidenced by the low incidence reported in some series of cases. Hyman, in 1918, presented three cases of renal tuberculosis in children of 10 and 11 years of age and stated that he had seen ten cases of children under 18 with surgical caseocavernous renal tuberculosis. Braasch, in 1920, in reviewing 532 surgical records of the Mayo Clinic on operations for renal tuberculosis from 1894 to 1918, found that two patients fell in the 0 to 10-year group; and 37 cases occurred in the second decade.

Beer, in 1930, wrote that surgical tuberculosis was rare in the young, and in his series of 280 cases of renal tuberculosis there were thirty cases under 20 years of age.

In 1931, I reported eight cases of renal tuberculosis in children up to the age of 14 years, five requiring operation, and in 1936, forty-three cases of renal tuberculosis, fifteen of them occurring before 15 years of age and twenty-eight between 15 and 21.

One must bear in mind the possibility of renal tuberculosis in children who present persistent pyuria and relapsing pyelitis. Careful examination should be made of every case of "chronic" pyuria. However, in the so-called silent renal tuberculosis, no symptoms may appear until the lesion in the parenchyma is far advanced. A perirenal abscess in children, especially one that is followed by a persistent sinus, should always arouse one's suspicions that the underlying cause may be renal tuberculosis. Not infrequently this disease runs a silent course and is discovered during the treatment for other tuberculous lesions. Children have been under treatment for tuberculosis of the bones and joints who had no urinary symptoms but who, during their period of hospitalization, had a persistent pyuria. Repeated studies of the urine showed the presence of the tubercle bacillus. Urologic studies of these children showed rather well-developed, and sometimes far-advanced renal tuberculosis, in spite of the fact that these children never had any urinary symptoms. After establishing the fact that the tuberculosis was unilateral, nephrectomy was carried out. There was no mortality, in spite of the fact that these patients had extensive bone and joint disease.

The diagnosis of renal tuberculosis can be made more readily if the investigation includes a complete physical examination, which may show tuberculous infection existing elsewhere in the body, and repeated studies of the urine show the presence of the tubercle bacillus. The presence of pus and tubercle bacilli calls for cystoscopic examination and ureteral catheterization with careful studies for the presence in one or the other kidney of the tubercle bacillus; smears, cultures, and guinea pig inoculations are carried out as a routine procedure.

Intravenous urography often gives definite information, especially in the well-developed cases. In the early cases a small lesion may be overlooked in the intravenous pyelogram. If the diagnosis of unilateral, renal tuberculosis is made from the urologic examination, one should rarely resort to retrograde pyelography.

Bilateral renal tuberculosis is not amenable to surgical treatment and the prognosis is unfavorable. Once the diagnosis of chronic unilateral renal tuberculosis has been made, provided the opposite kidney is free of tuberculous disease, nephrectomy is the proper course to pursue.

URINARY CALCULI

Authors differ in opinion as to the frequency of calculi in the young. The consensus is that urinary calculus is seldom seen in the young in this country, undoubtedly due to better sanitation, improved dieteties, and better care on the part of the pediatrician. In contrast to the foreign literature, which is replete with reports on urinary calculi in children, the literature in this country is comparatively scant, but the condition occurs frequently enough to warrant its serious consideration.

During the nineteenth century urinary calculus was very prevalent among English children and Thompson found in a series of 2,583 cases that one-half

occurred in children under 16 years of age. Rafin, in 1911, reported a series of 322 cases of renal calculi in infancy, of which 139 were found at necropsy. Bokay, in 1912, collected 1,826 cases of urinary stone in children under the age of 15 years. Thompson, in 1921, reported that urinary calculus was found in 25 per cent of the children in China. Noble, in 1931, also found 22 per cent of children under 11 years of age affected in Thailand; Assenfeldt of Austria, found 77 per cent of a series of cases occurring in children.

No such consistently high incidence is found in the American literature. Hill and Stevens in 1920 were able to cite 320 cases of renal calculus, one-half of which were necropsy findings; of these 140 were in children under 1 year of age. In 1922, Thomas and Tanner collected reports from members of the American Urologic Association of 203 cases of urinary lithiasis in the young; of these 112 were discovered with the roentgen ray. Bugbee and Wollstein, in 1924, in 4,903 necropsies found calculi in thirteen infants. Hagar, in 1927, found in a series of 3,295 cases of children under 15 years, bladder stones in eleven of 674; ureteral stones in seven of 813; and kidney stones in fifteen of 1,808. In 1930, Campbell reported thirty cases; seventeen of these were found at autopsy.

In 1931, I reported six cases of urinary calculus in children, and in 1936, published a study of twenty-one children under 13 years of age who had stone in the urinary tract, and concluded that it is a relatively uncommon disease in this country.

Tudor, in 1943, found that seven patients among 10,650 children admitted to the Duke Hospital had vesical stones, and stated that in America less than 2 per cent of the afflicted persons are children.

The cause of primary urinary calculus is unknown. Many theories have been presented as to the etiology of stone such as familial and racial influences, geographical locations, diet, and metabolic disturbances. Family history is of great importance in one type of calculus, namely, in the patient with cystine stone, since it is well known that in this type of stone, other members of the family may have cystine stones or cystinuria. In 1916, I reported two cases in twin brothers of cystinuria complicated by cystine stones in the bladder, and in 1930, three patients, one of which was in a male aged 12. Many members of the families of these cases showed the presence of cystine in the urine.

In the very young, the symptoms of stone are abdominal pain, vomiting, diarrhea, convulsions. As the gastrointestinal symptoms are very prominent, the presence of urinary calculi is not suspected, and they are found only on routine x-ray examination.

Pyuria is the major symptom of urinary stone in children. This has been stressed by Hyman (1926), who found it to be present in 30 to 50 per cent of his cases, and Thomas and Tanner (1922) in 31 per cent. Mertz and Lewis in 1934 reported pyuria in nine out of ten cases.

If there is hematuria accompanied by recurrent colicky pain, a stone should be suspected. Disturbances of micturition are frequency of urination, dysuria, and dribbling. Several children were admitted to the hospital with the diagnosis of acute appendicitis. The finding of fresh red blood cells in the urine led

to roentgen-ray examination with the resulting diagnosis of kidney or ureteral stones. In several patients the clew to the true pathology was the finding of cystine crystals in the urine.

Several patients with stone in the bladder with great frequency and dribbling were treated for a long time as cases of enuresis, without relief of symptoms.

Diagnosis in the child is the same as in the adult. Urinalysis, x-ray, intravenous pyelography, and cystoscopy should all be utilized.

The pathologic changes associated with the urinary calculus are the same in the child as in the adult. Stone may be accompanied by (1) hydronephrosis, (2) pyelonephritis, (3) pyonephrosis, or (4) perinephritic abscess.

Stones in the kidney that are obviously too large to pass, or that have produced hydronephrosis, stones that produce recurring attacks of chills and fever, hematuria, or that produce a chronic pyuria, should be operated upon.

It is possible to remove the stones by means of pyelotomy. This is easier than nephrotomy, less dangerous, carries with it a much lower operative mortality, and there is no danger of secondary hemorrhage, such as occurs with a nephrotomy.

Small stones in the ureter that show a tendency to progress down the ureter with each attack of renal colic, in cases where there is little or no infection, can be carried along with fluids and diuretics. If the urine shows cystine crystals, soda bicarbonate should be given. On the other hand, where the stones are obviously too large to pass and where a marked hydronephrosis exists, extraperitoneal ureterotomy is the operation of choice.

Small stones in the bladder can be treated with litholapaxy in a number of patients.

I would like to stress at this time the importance of clearing up residual infection after removal of the stone by surgical measures.

HYDRONEPHROSIS

Before the era of modern pediatric urology, most of the cases of hydronephrosis and hydroureter were not recognized, and the early literature deals with cases found at autopsy. The writings and investigations of Eisendrath, Henline, Hinman, Hyman, Kretschmer, Priestley, and many others have broadened our knowledge on this subject. As in other urologic diseases, it is imperative that early diagnosis be made so that early treatment can be instituted, if irreparable damage to the kidney is to be prevented.

There is no typical symptom-complex of hydronephrosis, and many times the disease runs a silent course. In some cases of indefinite and obscure abdominal pain, the presence of hydronephrosis is found during routine urologic examination. As a rule, most of these cases come to the attention of the physician after the onset of infection. When infection supervenes, patients have chills and fever, frequency of urination, and pyuria. Because of the presence of pyuria with chills and fever, many of these cases are erroneously diagnosed as acute pyelitis or acute cystitis.

Hydronephrosis due to adhesions in children is rare but does occur (Fig. 6).

Any patient suffering from recurring attacks of pyuria or in whom the pyuria does not respond to the usual medical management should be subjected to a complete urologic study. When the hydronephrosis is large, a palpable swelling in the renal area is often present at the first examination. When bilateral hydronephrosis is present, the condition may be confused with Wilms' tumor.

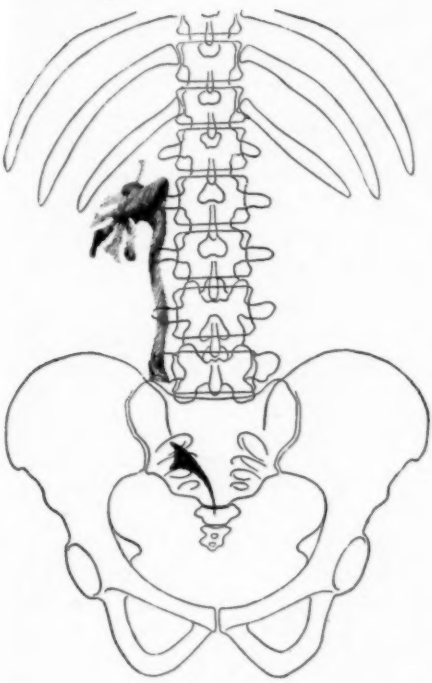


Fig. 6.

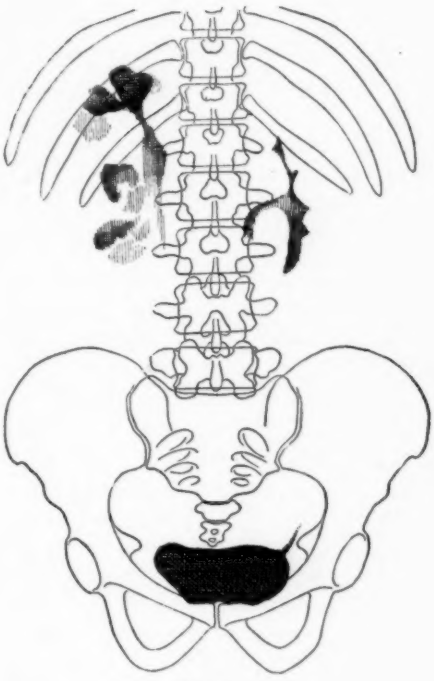


Fig. 7.

Fig. 6.—Hydronephrosis due to a dense, fibrous band at the sacral level.

Fig. 7.—Hydronephrosis in a double kidney with severe infection resulting in death of the patient.

Hydronephrosis and hydroureter may result from the following:

1. Obstructions in the lower urinary tract anywhere along the course of the urethra from the external meatus to and including the vesical neck. The most common obstructions of the posterior urethra and vesical neck are contracted vesical neck, posterior urethral valves, cysts and hypertrophy of the verumontanum, strictures of the urethra, and median bars. In 1937 I found sixteen in 101 cases of hydronephrosis associated with bladder neck obstructions, nine of which were due to congenital valves, three due to stricture of urethra, two to median bar, and two to contracted bladder neck.

2. Obstruction at the ureterovesical junction. Narrowing or obliteration of the ureter is one of the frequent causes of hydronephrosis and hydroureters. Cases have been reported by Buerger (1914), Kakels (1918), Wason (1920), Mixter (1922), Hahn (1924), Campbell (1933), and Hinman (1929). In 1933, I became interested in determining whether or not hydronephrosis was due to stricture of the vesical end of the ureter in the generally accepted interpretation of that word, and reported on fifteen cases. Stricture was present in only three patients, all of whom had an anomalous insertion of the ureter and the twelve remaining patients showed that hypertrophy of the muscular coat of the ureter was the cause of the obstruction.

Obstruction to the flow of urine at the ureterovesical junction may also be due to ureterocele or cystic dilatation of the ureter, of which I have seen six examples, one of which has been previously mentioned in this paper.

Bray, in 1939, reported two cases: in one there was a hypoplastic right kidney and hydronephrosis of the left kidney with strictures at the ureteropelvic and ureterovesical junctions; in the second there was bilateral congenital stricture of the ureteropelvic junction. Henline and Menning, in 1943, reported four children in whom the hydronephrosis was caused by ureteropelvic obstruction due to intrinsic stenosis. They stress the fact that many times several factors are present in causing an obstruction of the ureteropelvic junction and that it is important that the primary cause be corrected, as too frequently only the secondary factor is taken care of.

3. Obstruction at the ureteropelvic junction is not uncommon and may be due to either aberrant blood vessels, fibrous adhesions around the ureteropelvic junction and strictures at the ureteropelvic junction, or, occasionally, stone in the ureteropelvic junction.

Since Boogaard's description (1857) of the kinking of the ureter around an anomalous vessel, no unanimity of opinion prevails as to the role played by the aberrant renal vessel in hydronephrosis. Some authors believe hydronephrosis results from direct compression of the ureter by the vessels; others are of the opinion that there is some renal ptosis which in turn causes the aberrant vessel to compress the ureter; and there are those who think that there must exist a combination of factors, consisting of a movable kidney plus a fixed point caused by a vessel or band in the ureter either at, or in close proximity to, the ureteropelvic junction. There are some who believe that the hydronephrosis is not caused by the aberrant vessel and the presence of a hydronephrosis should not be ascribed to the presence of an aberrant artery.

The finding of anomalous renal vessels causing upper urinary obstruction is not frequent in children. Cases have been reported by Campbell (1933), Jewett (1939), Fite (1940), White and Wyatt (1942), and Moore (1942).

4. Pathologic conditions extrinsic to the urinary tract, i.e., pressure on the ureter from without. This is rarely found in children and is generally associated with retroperitoneal tumors such as large sarcomas and lipomas (Fig. 8). A recent case reported by Kereszturi in 1940 was that of an imperforate hymen which caused hydrocolpos in early infancy, and this in turn, through pressure

on the urinary tract, led to bilateral hydroureter and hydronephrosis, pyuria, and bacilluria. Retroperitoneal tumors may cause marked displacement of the kidney and ureter without hydronephrosis (Figs. 9 and 10).

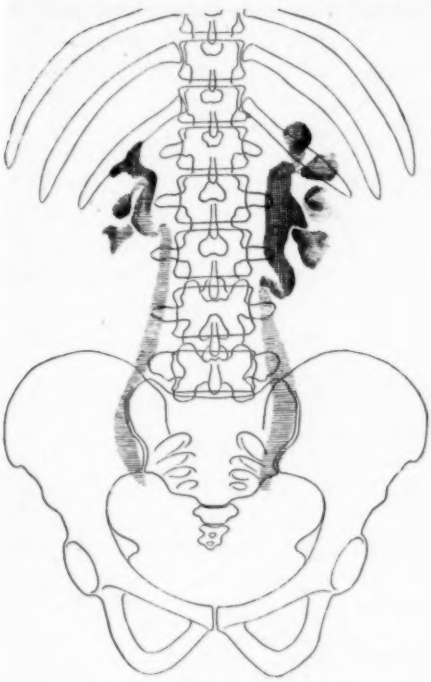


Fig. 8.

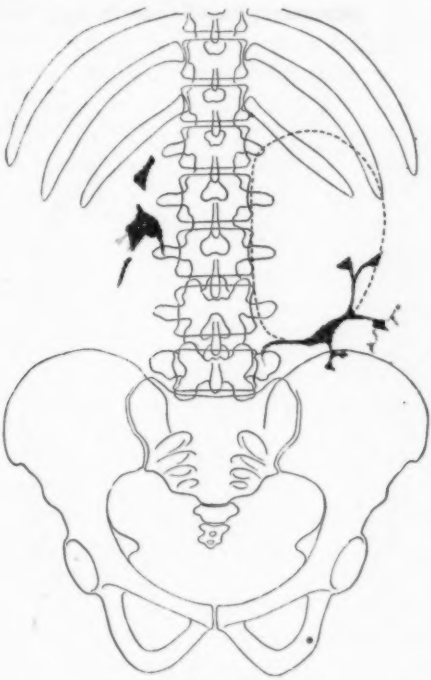


Fig. 9.

Fig. 8.—Bilateral hydronephrosis with lateral displacement of the ureters due to a retroperitoneal tumor.

Fig. 9.—Marked displacement of the kidney by a retroperitoneal tumor without hydronephrosis.

5. Hydronephrosis due to lesions of the central nervous system, such as one sees in spina bifida in children, where enormous hydronephrosis develops, and the nervous influence in adults, such as tabes dorsalis and spinal cord changes in pernicious anemia. These cases of hydronephrosis are explained on the basis of neuromuscular dysfunction without an anatomic explanation for its development. The hydronephrosis may be unilateral or bilateral. Generally, it is bilateral.

Treatment.—Treatment naturally depends on the cause of the condition. Obstructions in the lower urinary tract are removed by appropriate surgical measures as discussed previously in this paper in the section on obstructions of the lower urinary tract.

Strictures at the ureterovesical junction respond well to ureteral dilatation. The treatment of obstructions at the ureteropelvic junction depends on the

cause of the obstruction and generally requires surgical intervention. In some cases ureteral dilatation may be tried.

Stones naturally must be removed, preferably through a pyelotomy incision. Aberrant blood vessels may be divided. So-called strictures may be treated by surgical methods in which the various plastic operations are employed. Recently, there has been a tendency to employ the Rammstedt type of operation.

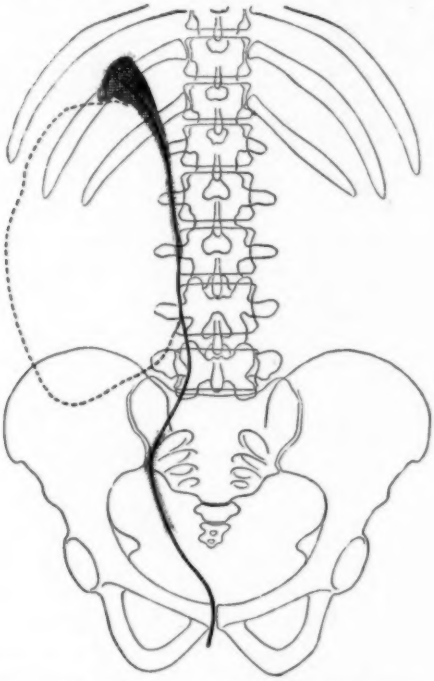


Fig. 10.—Upward displacement of kidney by a retroperitoneal tumor without hydronephrosis.

TUMORS OF THE URINARY TRACT

Tumors of the genitourinary tract in infancy and childhood, with the exception of kidney neoplasms, are rare.

Bladder Tumors.—Most of the literature dealing with bladder tumors concerns reports of a single case, together with an extensive review of the literature. The common bladder tumor in infancy and children is the sarcoma.

Excellent reviews on bladder tumors in the young have appeared since O'Neill's résumé in 1915 and Deming's report in 1924 of sixty-four authentic cases occurring in the first decade of life, including two of his own. Beer, in 1930, observed no bladder tumors in children in 500 personal cases. Rathbun, in 1937, covered seventy-five cases from the literature and reported a personal observation of hemangioma of the bladder in a 27-month-old baby. Segal and

Rink, in 1942, covered the literature on cavernous hemangioma of the bladder since 1869 and found forty-one cases, fourteen patients being under 20 years of age. They added to this figure their own case in a boy 15 years old.

Mertz and Hamer, in 1938, reporting on 167 patients, had two cases of bladder tumors in children, one a sarcoma and the other a chloroma. Campbell has seen three cases of bladder tumors in the young and another case where a sarcomatous nodule in the bladder was part of a generalized metastasis.

Dean, in 1940, remarked on the rarity of vesical tumors in childhood. From his study of published reports and records of the Memorial Hospital for Cancer and Allied Diseases in New York he found an approximate incidence of one bladder tumor in a child to each 950 bladder tumors in adults, mainly sarcomas.

Chalkley and Bruce, in 1942, reported a neurofibromatosis of the bladder in a 9-year-old boy, and found only one other case recorded (by Kass) occurring in a child.

Crane and Tremblay, in 1943, published an exhaustive survey since 1905 on sarcoma of the bladder and found thirty cases reported in children from one to nine years, and nine cases from 10 to 19 years of age.

I have seen only one tumor of the bladder in a child. This was an angioma of the bladder. The tumor was destroyed through the cystoscope with the high frequency current. My experience on the rarity of bladder tumors in children coincides with the experiences of other urologists.

Hematuria is the most frequent symptom of vesical tumor in children. When the disease is well advanced, interference with urination, which may result in an overdistended bladder, takes place. Many of these tumors develop "silently." On occasion, the tumor has been discovered in female infants only when it protrudes from the urethral meatus. The diagnosis is made by cystoscopic examination. Unfortunately, when these patients are presented for examination, the tumor has progressed so that the general health of the child is poor and the possibility of surgery affecting a cure is exceedingly remote. However, because clinical experience with irradiation is meager, little information is available regarding the radiosensitivity of these tumors.

It is to be hoped that, if we bear the possibility in mind that children with hematuria might have a tumor of the bladder, the patients will be given the benefit of a cystoscopic examination and these tumors will be recognized early, i.e., when they are small, so that the children can have the benefit of radical surgery.

Tumors of the Kidney.—It is only recently that the subject of renal tumors has received a good deal of attention.

Before the advent of pediatric urology, kidney tumors in children received scant attention. The nomenclature was confusing, the diagnosis was generally made late, and the operative mortality was very high. As a result of modern urologic diagnostic methods, the urologist, and then the pediatrician, became greatly interested. As more and more of these patients were operated upon,

the interest of the clinician and the pathologist in the pathology of these tumors was awakened, and finally the roentgenologist was drawn into the picture, not only in the interpretation of the pyelograms, but in therapy as well.

No longer are indefinite and confusing terms used to describe this entity, but instead it has been definitely established that these tumors are almost always of the type first described by Wilms and are now called Wilms' tumors.

Wilms' tumors are the most common malignant tumor of the genitourinary tract in children. The great proclivity of infants and children to malignant tumors of the kidney and the eye is in marked contrast to the rarity of these tumors in the adult. These tumors occur in the very young, although cases have been reported in the adult. Because of this fact, it is universally agreed that they are congenital in origin. There is, on the other hand, no agreement concerning the genesis of Wilms' tumors, and many theories have been advanced, among them being: (1) origin from aberrant germ plasm of the primordial segments; (2) origin from the wolffian body (this theory has such adherents as Ebert, Doederlein, and Birch-Hirschfeld; Dean and Pack have never been able to ascertain any wolffian remnants in the human kidney, and discard this theory as untenable); (3) origin from renal blastema or nephrotome, which theory Wilms upheld; (4) origin from endothelial cells, which embraces theory of metaplasia to explain the variegated microscopic picture (advanced by Brosin in 1884). Dean and Pack believe that these embryonal renal adenosarcomas originate at different developmental periods of the embryo, the renal blastema or nephrotome being the predominant contributing structure. Geschickter and Widenhorn (1934) state that the earlier theories of pathogenesis relating Wilms' tumor to the wolffian body or to aberrant rests from the sclerotome or myotome have been superseded by data relating these tumors to embryonic nephrogenic tissue (the relationship first set forth by Muus). Weisel, Dockerty, and Priestley of Mayo Clinic, from the various theories presented, came to the thought that mixed renal neoplasms possibly originate (a) from embryonic cellular rests; (b) from one or more germ layers (teratomatous); or (c) from the mesenchyma of the embryonic kidney, through a process of perverted growth and metaplasia.

Dean and Pack, in 1932, studied 19,129 cases of neoplastic diseases at the Memorial Hospital for Cancer and Allied Diseases from January, 1917 to January, 1929, inclusive. Of these 16,565 were malignant, and the sixteen embryonal adenosarcomas of the kidney reported in this study constituted 0.083 per cent of all admissions and 0.096 per cent of all malignant tumors treated during this period. Later in 1940, Dean stated that twenty-four cases of Wilms' tumor of kidney were seen so far at the Memorial Hospital. Other reported cases of Wilms' tumor in children are those by Campbell (1937), Mertz and Hamer (1938), and Weisel and associates (1940).

Of the three constant symptoms of renal tumors in general, namely, a visible or palpable tumor, hematuria, and pain, only the first is constant in malignant renal tumors of children. The abdomen swells gradually, becoming

asymmetrically or symmetrically global. Fever is next in constancy and may be intermittent, remittent, moderate, or high.

In contrast to the hypernephroma, the Wilms' tumor seldom causes hematuria. In the adult, hematuria is the common symptom of renal tumor. In children hematuria is rare. I have only seen one case of Wilms' tumor in a child in whom a history of hematuria was obtainable. Hematuria, when present, is usually due to hemorrhage from the parenchyma of the congested kidney rather than from the tumor itself.

Unfortunately, the common condition which brought the patients to me was the presence of an abdominal tumor, often found by the mother or nursemaid, generally when the tumor had reached an enormous size. In contrast, it is to be stated that many have been recognized by the pediatrician during a routine physical examination.

The absence of pain also tends to prevent its early discovery. Pain, when present, is of the colicky type. Pressure symptoms appear in accordance with the growth of the tumor, e.g., cough, dyspnea, ascites, edema, constipation. Vague gastrointestinal symptoms bring the child to the doctor, who, on palpation, finds a good-sized abdominal mass. In an early stage, tumors on the right may simulate appendicitis. As pain is absent early in the course of the disease, there is nothing to direct attention to the kidney. In two series of cases, a total of twenty-four patients, reported previously by me, the one common symptom was palpable tumor, which was present in every instance. Fever was present in eleven instances, abdominal pain in eight, loss of appetite in seven, loss of weight in six, vomiting in four, frequency in two, burning in one, and hematuria in one.

Differential diagnosis concerns excluding other renal lesions, of which hydronephrosis is the commonest, and other retroperitoneal lesions, such as sarcoma and lipoma, which can be excluded rather easily. In other retroperitoneal tumors, the course of the ureter as shown with the shadowgraph catheter is quite typical. In these cases there is a lateral displacement of the ureter.

Diagnosis should be based on the presence of a palpable tumor and changes in the urogram. Excretory urograms will show deformity of the pelvis and calyces. Ureteral catheterization is to be carried out to determine the functional capacity of the kidney. A plain roentgenogram of the chest is indicated in each case to rule out the possibility of metastasis, and a plain film of the abdomen will rule out stone in the urinary tract. It is the consensus of opinion that under no circumstances should one incise a Wilms' tumor for biopsy, as this destroys the capsule of the tumor and encourages more rapid and widespread growth. Also, frequent palpation of the tumor is inadvisable as metastases from Wilms' tumor are generally blood borne. Once the diagnosis is made, there should be no more palpation.

An interesting phenomenon occurs in the changes in the pyelograms made at the end of the preoperative radiation. This phenomenon was described by me in a previous publication. In the cases that respond to radiation, that is,

in which the tumor shows marked regression in size, the pyelogram has a normal or a nearly normal configuration.

There are still some differences of opinion regarding treatment, and these fall into three groups:

1. Those who believe in roentgen therapy alone. They are in the minority and some of them now advocate surgery if there is a cessation in the diminution of the size of the tumor. It is to be remembered that after the tumor has diminished in size following radiation therapy, should it then begin to increase in size, the tumor is no longer sensitive to radiation.

2. By far the largest number of urologists believe in a combination of deep therapy and nephrectomy. A course of deep therapy is given before operation. Although not all Wilms' tumors do respond, the majority show a rapid diminution in size. When the tumor no longer diminishes in size under roentgen treatment, having become stationary, nephrectomy is carried out at once, and this is followed with a course of postoperative radiation. This technique has resulted in a great reduction of the operative mortality, which today is practically nil, since the diminution in size of the tumor makes nephrectomy a simple procedure.

3. The third group perform nephrectomy as soon as the diagnosis is made. Ladd and White believe that the chance of survival for a patient with embryoma of the kidney is far greater if the policy of immediate operation is adopted rather than the policy of delayed operation following roentgen therapy.

It seems wise to issue a word of caution in the study of these cases. Once the diagnosis has been made, I do not believe that these tumors should be subjected to repeated palpation by the house staff and the students, since repeated and often severe manipulation may be a factor in the dissemination of tumor cells and hence a factor in metastasis.

SUMMARY

1. Age is no longer a contraindication to complete urologic examination in infants and children.

2. The persistence of pus in the urine demands complete urologic examination.

3. Relapsing or recurring attacks of cystitis and pyelitis demands complete urologic examination.

4. Lesions of the urinary tract in children are the same as in adults.

5. Certain lesions are seen more frequently in children than in adults, namely, Wilms' tumors.

6. Lesions of the bladder and prostate common in the adult are uncommon in children.

7. The splendid early cooperation between pediatrician and urologist has resulted in a shortened period of morbidity and in preventing destruction of vital organs.

REFERENCES

Beer, Edwin: Cystoscopy and Ureteral Catheterization in Young Children, Am. J. Surg. 25: 79, 1911.
Beer, Edwin: Some Observations on Contracture of Neck of Bladder, New York M. J. 115: 536, 1922.
Beer, Edwin: The Importance of the Recognition of Surgical Diseases in the Urinary Organs of Children, Internat. Clin. 3: 272, 1923.
Beer, E.: Chronic Retention of Urine in Young Boys Due to Obstruction at the Neck of the Bladder, Ann. Surg. 79: 264, 1924.
Bigler, J. A.: Anamolies of Urinary Tract in Children, Frequency and Types in Consecutive Necropsy Series, Am. J. Dis. Child. 38: 960, 1929.
Braasch, W. F., and Hendrick, J. A.: Renal Cysts, Simple and Otherwise, J. Urol. 51: 1, 1944.
Braasch, W. F.: Surgical Renal Tuberculosis, Am. J. M. Sc. 159: 8, 1920.
Brown, R.: Cystotomy for Stone in Children, Am. J. Surg. 48: 342, 1940.
Bugbee, H. G., and Wollstein, M.: Surgical Pathology of the Urinary Tract in Infants: Based on a Review of 4,903 Necropsies, J. A. M. A. 83: 1887, 1924.
Bugbee, H. G., and Wollstein, M.: Retention of Urine Due to Congenital Hypertrophy of the Verumontanum, J. Urol. 10: 477, 1923.
Buerger, Leo: Congenital Hydroureter and Hydronephrosis, Internat. Clin. 4: 243, 1914.
Butterfield, P. M.: Experiences With New Baby Cystourethroscope, Am. J. Surg. 8: 102, 1930.
Butterfield, P. M.: A New Double Catheterizing Cystoscope for Use in Infants and Children, J. Urol. 13: 493, 1925.
Campbell, M. F.: Pediatric Urology, New York, 1937, The Macmillan Company.
Campbell, M. F.: Chronic Pyuria in Juveniles, J. Urol. 31: 205, 1934.
Campbell, M. F.: Urinary Calculi in Infancy and Childhood, J. A. M. A. 94: 1753, 1930.
Campbell, M. F.: Urogenital Tuberculosis in Infants and Children, New York State J. Med. 38: 631, 1938.
Campbell, M. F.: Vascular Obstruction of Ureter in Juveniles, Am. J. Surg. 22: 527, 1933.
Campbell, M. F.: Urological Instrumentation in Infants and Children, Urol. & Cutan. Rev. 35: 28, 1931.
Campbell, M. F., and Lyttle, J. D.: Ureteral Obstruction in Infancy; Study of 74 Cases, J. A. M. A. 92: 544, 1929.
Casper, L.: Handbuch der Cystoscopie, Leipzig, 1911.
Caulk, J. R.: Urinary Obstructions in Infants and Children, Surg., Gynec. & Obst. 63: 80, 1936.
Caverly, C. S.: Anomalous Condition of the Kidneys, Am. Med. 7: 296, 1904.
Chalkley, T. S., and Bruce, J. W.: Neurofibromatosis of Bladder in a 9-Year-Old Boy, J. Pediat. 20: 632, 1942.
Chalkley, T. S., and Sutton, L. E., Jr.: Infected Solitary Cyst of Kidney in Child, With Review of Literature, J. Urol. 50: 414, 1943.
Coppridge, W. M.: Tumors of the Bladder, Virginia M. Monthly 71: 500, 1944.
Collins, A. N.: Urinary Lithiasis, in Abt's Pediatrics, vol. 4, Philadelphia, 1924, W. B. Saunders Company, p. 938.
Cone, R. E.: Surgical Management of Cryptorchidism, Ann. Surg. 119: 591, 1944.
Corbus, B. C.: Smaller Children's Observation, Irrigating and Catheterizing Cystoscope, J. Urol. 23: 709, 1930.
Counseller, V. S.: Ten Years' Experience in Management of Cryptorchidism, J. Urol. 46: 722, 1941.
Crane, A. R., and Tremblay, R. G.: Primary Osteogenic Sarcoma of the Bladder, Ann. Surg. 118: 887, 1943.
Dean, A. L., Jr., and Pack, G. T.: Embryonal Adenosarcoma of Kidney, J. A. M. A. 98: 10, 1932.
Dean, A. L.: Cancers of the Genitourinary Organs in Children; in Dargeon, Harold W.: Cancer in Childhood, St. Louis, 1940, The C. V. Mosby Company.
Dean, A. L.: Cancers of the Genitourinary Organs in Children, J. Pediat. 15: 340, 1939.
Dean, A. L.: Treatment of Tumors of Genitourinary Organs, S. Clin. North America 20: 409, 1940.
Dean, A. L., and Pack, G. T.: Embryonal Adenosarcoma of Kidney, J. A. M. A. 98: 10, 1932.
Deming, C. L.: Congenital Sarcoma of Kidney in a Child of 29 Days, J. A. M. A. 80: 902, 1924.
Ehrich, W. S.: Congenital Obstruction at Urethro-vesical Orifice, J. Urol. 13: 471, 1925.
Eisendrath, D. N.: The Clinical Importance of the Horseshoe Kidney, Surg., Gynec. & Obst. 18: 467, 1912.
Eisenstaedt, J. S., Appel, M., and Fraenkel, M.: The Effect of Hormones on the Undescended Testis; Experimental and Clinical Study, J. A. M. A. 115: 200, 1940.
Fite, E. H.: Conservative Surgery in Management of Hydronephrosis, J. Urol. 43: 177, 1940.
Fowler, Major F.: The Diagnosis and Management of Congenital Valves at Vesical Neck; Report of Cases, J. Urol. 49: 178, 1943.

Grantham, W. L., and Bunts, R. C.: Congenital Obstruction of Bladder Neck, South. M. J. **33**: 939, 1940.
Grant, O.: Obstructions at the Vesical Neck in Children, J. Urol. **40**: 114, 1938.
Gutierrez, R.: in Cabot's Modern Urology, Philadelphia, 1936, Lea & Febiger.
Hahn, E. V.: Congenital Hydronephrosis; a Review of the Literature With a Report of Two Cases, Arch. Surg. **9**: 256, 1924.
Hager, B. H., and Magath, T. B.: Formation of Vesical Calculi, J. A. M. A. **90**: 266, 1928.
Hand, A., Jr.: Congenital Anomalies of the Kidney, Tr. Path. Soc. Phila. **18**: 323, 1898.
Hendrickson, F. C., and Simon, K.: Congenital Contracture of the Vesical Neck, J. Urol. **42**: 140, 1939.
Henline, R. B., and Menning, J. H.: Management of Hydronephrosis Due to Ureteropelvic Obstruction; Preliminary Report, J. Urol. **50**: 1, 1943.
Hepler, A. B.: Congenital Valves of Posterior Urethra, Northwest Med. **26**: 69, 1927.
Hess, E.: Unilateral Fused Kidney With Nonobliteration of the Hypogastrics, J. Urol. **29**: 695, 1933.
Hess, E., and Peters, C. O.: Congenital Valves of Posterior Urethra; Report of Two Cases, Pennsylvania M. J. **35**: 460, 1932.
Higbee, D. R.: Congenital Renal Hypoplasia Associated With Hypertension; Report of Two Cases, J. Urol. **51**: 466, 1944.
Higgins, C. C., and Shively, F. L., Jr.: Malignant Renal Neoplasms in Children, Arch. Surg. **42**: 386, 1941.
Higgins, C. C.: Transplantation of the Ureters Into the Rectosigmoid; Experimental and Clinical Consideration, J. Urol. **37**: 90, 1937.
Higgins, C. C.: Ureterointestinal Implantation, Surgery **2**: 1, 1937.
Higgins, C. C.: Transplantation of the Ureters Into the Rectosigmoid in Infants; Review of Nineteen Cases, J. Urol. **50**: 657, 1943.
Hill, M. C., and Stevens, A. R.: Nephrolithiasis in a Girl of Three Years, Arch. Pediat. **37**: 615, 1920.
Hinman, F.: The Cystoscopic Study of Urologic Conditions in Children, Am. J. Dis. Child. **17**: 305, 1919.
Hinman, F.: Principles and Practice of Urology, Philadelphia, 1935, W. B. Saunders Company.
Hinman, F., and Kutzmann, A. A.: Congenital Valvular Obstruction of the Posterior Urethra, J. Urol. **14**: 71, 1925.
Hinman, F.: Obstructive Hydroureteral Angularity With Hydronephrosis in Children; Surgical Treatment, Arch. Surg. **18**: 21, 1929.
Hinman, F., and Kutzmann, A. A.: Malignant Tumors of Kidney in Children, Ann. Surg. **80**: 569, 1924.
Howard, L. L.: Double Kidney and Double Ureters With Ectopic Ending of One Ureter, J. Urol. **49**: 436, 1943.
Hyman, A.: Clinical Aspects of Surgical Disease of the Urinary Tract in Children, J. Urol. **16**. 259, 1926.
Hyman, A.: Surgical Diseases of the Urinary Tract in Children, Am. J. Dis. Child. **15**: 116, 1918.
Jewett, H. J.: Accessory Renal Vessels; Their Influence on Certain Cases of Hydronephrosis, Surg., Gynec. & Obst. **68**: 666, 1939.
Knox and Sprunt: Am. J. Dis. Child. **4**: 137, 1912.
Kakels, M. S.: Transperitoneal Nephrectomy in Infants for Large Congenital Hydronephrosis, Surg., Gynec. & Obst. **26**: 681, 1918.
Kereszturi, C.: Imperforate Hymen Causing Hydrocolpos, Hydroureter, Hydronephrosis, and Pyuria; Its Occurrence in Infant, Am. J. Dis. Child. **59**: 1290, 1940.
Kretschmer, H. L., and Helmholz, H. F.: The Treatment of Pyelitis in Infancy and Childhood, J. A. M. A. **75**: 1303, 1920.
Kretschmer, H. L.: Diverticulum of the Bladder in Infancy and in Childhood, Am. J. Dis. Child. **48**: 842, 1934.
Kretschmer, H. L.: Diseases of the Urinary Tract in Infancy and Childhood, Surg., Gynec. & Obst. **53**: 129, 1931.
Kretschmer, H. L.: Urologic Problems in Infancy and Childhood, Am. J. Dis. Child. **33**: 952, 1927; J. Urol. **18**: 433, 1927.
Kretschmer, H. L., and Hibbs, Wm. G.: A Study of the Vesical End of the Ureter in Hydronephrosis; a Report of Fifteen Cases, Surg., Gynec. & Obst. **57**: 170, 1933.
Kretschmer, H. L.: Malignant Tumors of the Kidney in Children, J. Urol. **39**: 250, 1938.
Kretschmer, H. L., and Pierson, L. E.: Congenital Valves of the Posterior Urethra, Am. J. Dis. Child. **38**: 804, 1929.
Kretschmer, H. L.: Stone in the Urinary Tract in Children; a Critical Study of Twenty-one Cases, Am. J. Dis. Child. **52**: 513, 1936.
Kretschmer, H. L.: Hydronephrosis in Infancy and Childhood; Clinical Data and a Report of 101 Cases, Surg., Gynec. & Obst. **64**: 634, 1937.
Kretschmer, H. L.: Tuberculosis of the Kidney in Childhood and Adolescence, Illinois M. J. **70**: 119, 1936.

Kretschmer, H. L., and Hibbs, W. G.: Mixed Tumors of Kidney in Infancy and Childhood; Study of 17 Cases, Surg., Gynec. & Obst. **52**: 1, 1931.
Kretschmer, H. L.: Urology in Children, Surg., Gynec. & Obst. **71**: 684, 1940.
Kretschmer, H. L.: Adenomyosarcoma of Kidney (Wilms' Tumor); Report of Three Cases, Arch. Surg. **41**: 370, 1940.
Kretschmer, H. L.: Supernumerary Kidney; Report of Case With Review of Literature, Surg., Gynec. & Obst. **49**: 818, 1929.
Kretschmer, H. L.: Tuberculosis of Kidney; Critical Review Based on Series of 221 Cases, Am. J. Surg. **9**: 221, 1930.
Kretschmer, H. L.: Diseases of Urinary Tract in Infants and Children, Proc. Staff Meet., Mayo Clin. **5**: 342, 1930.
Kretschmer, H. L.: Chronic Renal Tuberculosis, J. Iowa M. Soc. **21**: 336, 1931.
Kreutzmann, H. A. R.: Bilateral Ureteropelvic Stricture; Hydronephrosis and Multiple Renal Calculi in a Child, J. Urol. **49**: 464, 1943.
Ladd, W. E., and White, R. R.: Embryoma of Kidney (Wilms' Tumor), J. A. M. A. **117**: 1858, 1941.
Ladd, Wm. E., and Lanman, T. H.: Exstrophy of the Bladder, New England J. Med. **216**: 637, 1937.
Ladd, Wm. E., and Lanman, T. H.: Exstrophy of the Bladder and Epispadias, New England J. Med. **222**: 130, 1940.
Lowsley, O. S., and Kirwin, T. J.: A Clinical and Pathological Study of Congenital Obstruction of the Urethra; Report of Four Cases, J. Urol. **31**: 497, 1934.
Lowsley, O. S., and Butterfield, P. M.: Urologic Conditions Among Children, J. Urol. **16**: 415, 1926.
McCarthy, J. F.: Consideration of Newer Diagnostic and Surgical Procedures in Bladder and Posterior Urethra (Visualization as Applied to Urology), Proc. Internat. Assemb. Inter-State Post Grad. M.A., North America (1928), p. 197, 1929.
McKay, Robert W.: Obstructions of the Vesical Neck in Children, South. M. J. **33**: 377, 1940.
McKay, R. W.: Congenital Hypertrophic Ureteropelvic Obstruction, Am. J. Surg. **11**: 67, 1931.
Marquardt, C. R., and Frederick, A. J.: Congenital Imperforate Urinary Meatus, Urol. & Cutan. Rev. **47**: 78, 1943.
Martinson, H., and Reuben, M. S.: Congenital Hydronephrosis and Hydroureters, Thorium Intoxication, Autopsy, Arch. Pediat. **40**: 58, 1923.
Mathe, C. P.: Juvenile Tuberculosis of the Kidney; Diagnosis and Treatment, Surg., Gynec. & Obst. **63**: 283, 1936.
Mertz, H. O., Howell, R. D., and Hendricks, J. W.: Limitations of Irradiation of Solid Renal Tumors in Children, J. Urol. **46**: 1103, 1941.
Mertz, H. O.: Congenital Changes in Urinary Organs as They Influence Pyuria of Infancy and Childhood, J. Urol. **19**: 371, 1928.
Mertz, H. O., and Hamer, H. G.: Urology in Children, J. Urol. **39**: 548, 1938.
Mixter, C. G.: Tumors of the Kidney in Infancy and Childhood, Ann. Surg. **76**: 52, 1922.
Nation, E. F.: Renal Aplasia; Study of 16 Cases, J. Urol. **51**: 579, 1944.
Nitze, M.: Lehrbuch der Kystoskopie; ihre Technik und klinische Bedeutung, Wiesbaden, 1907.
O'Neil, R. F.: Bladder Tumors in the Young, Boston M. & S. J. **173**: 873, 1915.
Pace, J. M.: Bladder Neck Obstruction of Congenital Origin, Tr. South Central Section Am. Urol. A., 1940.
Pace, John M.: Congenital Bladder Neck Obstruction, Texas State J. Med. **40**: 322, 1944.
Portner, E.: Cystoskopie und Ureterenkatheterismus in der Kinderpraxis, Deutsche med. Wchnschr. **34**: 1851, 1908.
Powell, R. E.: Impaired Renal Function in Vesical Neck Obstruction, Surg. Clin. N. Am. **25**: 1033, 1945.
Powers, J. H., and Murray, M. F.: Juvenile Hypertension Associated With Unilateral Lesions of Upper Urinary Tract, J. A. M. A. **118**: 600, 1942.
Quinby, W. C.: Pyelitis in Children, J. A. M. A. **68**: 591, 1917.
Randall, A.: Congenital Valves of Posterior Urethra, Ann. Surg. **73**: 477, 1921.
Rathbun, N. P.: Primary Bladder Tumors in Infants and Young Children, With Report of Case of Hemangioma in Male Child 27 Months of Age, Surg., Gynec. & Obst. **64**: 914, 1937.
Ritter, J. S., and Kramer, S. E.: Congenital and Acquired Obstructions at Vesical Neck in Children, New York State J. Med. **43**: 2196, 1943.
Roos, A.: Polycystic Kidney; Report of Case Studied by Reconstruction, Am. J. Dis. Child. **61**: 116, 1941.
Rowe, E. W., and Frazer, M. D.: Roentgen Therapy of Wilms' Tumor, Radiology **42**: 107, 1944.
Schmidt, L. E.: Cystoscopy; Catheterization, in: Abt's Pediatrics **4**: 1157, 1924.

Segal, A. D., and Rink, H.: Cavernous Hemangioma of the Bladder, J. Urol. 47: 453, 1942.
Shands, H. C.: Simultaneous Occurrence of Polycystic Kidneys and Erythroblastosis Fetalis; Report of 3 Cases, Arch. Path. 40: 72, 1945.
Smith, Clinton K.: Urinary Calculi in Children, J. A. M. A. 91: 1431, 1928.
Smith, C. K.: Ureteropyelographic Postmortem Study of Infants and Children; Relation to Urology in Adults and Practical Application to Children, Tr. Sect. Urology, A. M. A., pp. 112-118, 1926.
Sprenger, A.: Urological Problems in Childhood, South. M. J. 25: 137, 1932.
Stevens, Wm. E.: Diagnosis and Treatment in Pathologic Conditions of Urinary Tract in Children, Modern Methods, J. A. M. A. 77: 1081, 1921.
Thomas, G. J., and Tanner, C. O.: Urinary Lithiasis in Children, J. Urol. 8: 171, 1922.
Thompson, G. J.: Urinary Obstruction of the Vesical Neck and Posterior Urethra of Congenital Origin, J. Urol. 47: 591, 1942.
Thompson, W. O., and others: Treatment of Undescended Testes With Anterior Pituitary-like Substance, Endocrinology 21: 220, 1937.
Thompson, W. O., and Heckel, N. J.: Endocrine Treatment of Cryptorchidism, J. A. M. A. 117: 1953, 1941.
Tudor, R. B.: Stones in Urinary Bladder in Children; Diagnosis and Treatment in 7 Cases, Am. J. Dis. Child. 65: 591, 1943.
Wason, I. M.: Report of a Case of Congenital Stenosis of Both Ureteral Orifices, J. Urol. 4: 123, 1920.
Weisel, W., Dockerty, M. B., and Priestley, J. T.: Wilms' Tumor of Kidney; Clinicopathologic Study of 44 Proved Cases, J. Urol. 50: 399, 1943.
White, R. R., and Wyatt, G. M.: Surgical Importance of Aberrant Renal Vessel in Infants and Children, Am. J. Surg. 58: 48, 1942.
Yardumian, K. Y., and Ackerman, M. A.: Congenital Polycystic Kidneys, Urol. & Cutan. Rev. 47: 147, 1943.
Young, H. H.: Practice of Urology, Philadelphia, 1926, W. B. Saunders Company.
Young, H.: Presentation of New Double Catheterizing Cystoscopes for Adults and for Infants, J. Urol. 27: 249, 1932.
Young, H. H., Frontz, W. A., and Baldwin, J. C.: Congenital Obstruction of the Posterior Urethra, J. Urol. 3: 289, 1919.

The Academy Study of Child Health Services

THE HISTORICAL BACKGROUND OF THE STUDY OF CHILD HEALTH SERVICES

In 1931, when the American Academy of Pediatrics was organized, there was a vast store of new knowledge in all fields of medicine. New skills and new techniques had been developed for the cure and prevention of disease. But the means of bringing these newly acquired medical skills to those who needed them had advanced little, if at all. For the most part, it was the wealthy and the very poor who benefited from the new advances in medical knowledge; the masses of people in between were left out of the new horizons in medical knowledge except at a crippling cost to themselves and their families. The immediate problem, therefore, which faced the medical profession at the time of the founding of the Academy was essentially a problem in the distribution of medical care.

How to make quality medicine available to all mothers and children regardless of wealth, race, or creed was a question of primary concern of the Academy at the time of its organization and has, either consciously or unconsciously, remained the chief preoccupation of the Academy during the fifteen years of its existence. The answers to this problem of distribution are not simple. In all times the more equitable distribution of wealth, of the products of the hands, of the benefits of science and of the quality care of the sick have been sought and not found. That failure presents no reason why the answers should not be continuingly sought.

That the Academy was seeking new answers is amply borne out in the first report of the Committee on Hospitals and Dispensaries. In June, 1931, Dr. Gerstenberger, Chairman of the Committee, recommended that the "Academy set about securing regularly accurate information as to the existing facilities and needs of hospitals in the United States and Canada caring for infants and children; of independent institutions and independent pediatric departments of general hospitals and of wards for infants and children existing as units or parts of medical services. This survey is to include medical, nursing, dietetic, social and administrative services." As this proposed survey covered between 6,500 and 7,000 hospitals having a certain relation to children, it led Dr. Grulee to remark that "Dr. Gerstenberger had bitten off a pretty large bite."

This report of the Committee on Hospitals and Dispensaries was sympathetically discussed and was then laid aside rather wistfully as being impractical at the moment. It is, however, notable in that it accurately foreshadowed an action which was to be taken by the Academy a dozen years later. Moreover, it outlined in some detail the lines of the study in which the Academy is at the moment engaged. All will agree that in 1931 the survey was not a practical project for the Academy to undertake. It was something like entering a newborn babe in an intercollegiate race. In view of the immaturity of the infant Academy, failure would have been a certainty, but it was proper to fix a goal, even that early, with the hope and expectation that the day would arrive when a winning race could be run.

The germ of the idea of a study of child health services appeared also in Dr. Isaac Abt's address which inaugurated the Academy in 1931. He stated that "The prime object of medical organization is the dissemination of medical knowledge." He urged that the educational qualifications of pediatricians be studied and that the improvement of the general standing of hospitals, the study of the nursing and social services, and the interest of the Academy in undergraduate and postgraduate instruction in pediatrics be fostered. He emphasized the importance of Dr. Grulee's report, which demanded that the Academy study the status of the general hospital and dispensary for sick children, the need of health clinics,

the desirability of a positive stand for the development of preventive mesaures against disease and infection, and many other points and objectives which the present Committee for the Study of Child Health Services has on its agenda of study.

Like a scarlet thread running through a bolt of cloth, the idea keeps reappearing in the discussions of the Executive Board and in committee reports. Like the "old man of the sea" the idea would not down until finally it became plain that if the Academy of Pediatrics were to fulfill its destiny, it had to undertake a survey of child health services throughout the nation. That 1944 was to be the year of decision was inherent in all its acts from the moment of birth. The Study of Child Health Services was no accident, nor was it the consequence of a sudden burst of energy. The twelve intervening years were the years of preparation to take on a task that had by its magnitude daunted every other medical group interested in the welfare of mothers and children.

As early as 1935, the Academy Committee on Child Health Relations urged that Academy groups undertake to inform themselves on the status of child health activities in their state, the provision for medical care and health supervision of children in institutions or under the care of agencies, both official and voluntary, the medical and health needs of children in their states, and the basic facts of mortality and morbidity among children in their state. The purpose of the resolution was "to appraise the work already done and to improve the health and medical care of children through cooperation" with all possible agencies.

The Committee on Medical Legislation, which was formed in 1935, has from the first been an active committee reporting on and analyzing all federal health bills introduced in Congress having to do with the medical profession. The Academy owes this Committee a deep debt of gratitude for the education given its members. The reports of 1936, 1939, 1943, and 1946 were all notable in forming the policies of the Academy. Again and again by direct statement and by implication, the point is stressed that the facts on which a wise and comprehensive health plan can be based are not known to the medical profession nor to any agency either public or private.

Dr. Wall's report to the Executive Board in June, 1944, on the EMIC program and the resulting recommendation that the special committee on the EMIC's program "include in its studies the question of facilities available for the health supervision of infants and for promoting the welfare of children" brought to a head a gathering storm of protest directed against the Children's Bureau. At about this time, attention was called to the fact that the functions of the Children's Bureau had been abruptly changed so that in 1944, it was an active factor in the practice of medicine throughout the United States, regulating fees and conditions of practice on a federal scale. It was at this June meeting of 1944 that the Academy nearly broke off relations with the Children's Bureau. This controversy called forth a letter from Dr. Grover Powers in defense of the Children's Bureau and caused Dr. Borden Veeder and Dr. Lee Forrest Hill to write an editorial in the December issue of the JOURNAL OF PEDIATRICS (1944) stating the position of the Academy not only in the matter of the EMIC's program, but also advocating a Federal Bureau of Health and foreshadowing the Study of Child Health Services.

The differences with the Children's Bureau and the proposed health bills in Congress were all to the good in so far as they made physicians not only take a stand, but, of what was of more importance, to think problems through. It was no longer enough to do a passable routine job, for it was necessary for physicians to orient into the general social scheme their ancient function of curing disease. The public was not only demanding care of high quality at the bedside but also they had a well-grounded suspicion that prevention of illness was even a better objective.

It is thus very clear that the Study of Child Health Services is no accident. Rather, it is an inevitable product of the Academy's development, waiting only on the Academy's growth to maturity and the logical timing of the effort. During its brief history, the Academy has been in agreement with the common longing for better maternal and child health programs

for all the people, but has been firm in its demand that hasty and poorly-conceived legislation be strictly avoided. An honest bill aimed at the improvement of medical care cannot be written until the facts are known. Any such bill should be based upon knowledge of what we have, what we lack, and what we need.

With the year 1944, the twelve years of preparation were ended and the Academy was ready to set out on the task of finding the facts, facts which should speak for themselves and write their own program of good health for all mothers and children.

MARSHALL C. PEASE, M.D., Historian

Academy News and Notes

The following members have been released from service:

Thomas A. Gibson, Winchester, Va.	*(Army)*
David W. Goltman, Memphis, Tenn.	*(Army)*
Harold Jacobziner, New York, N. Y.	*(Navy)*
H. A. Slesinger, Windber, Pa.	*(Army)*
Joseph McBride Sloan, Corpus Christie, Texas	*(Navy)*
Frederick F. Tisdall, Toronto, Ont.	*(R.C.A.F.)*
E. V. Turner, Columbus, Ohio	*(Navy)*
Raeburn James Wharton, Johnson City, N. Y.	*(Army)*

The Social Aspects of Medicine

Dear Dr. Park:

At the American Academy of Pediatrics Legislation Committee luncheon in Pittsburgh on February 25, it was suggested that the committee present a statement of basic principles that should govern our consideration of medical care plans.

In this connection it was pointed out that a committee of the Massachusetts Medical Society representing all shades of thought in the society was able to reach a unanimous conclusion concerning such basic principles.

I am enclosing a copy of these basic principles adopted by the Massachusette Medical Society, together with a practical application of these principles in an actual review of the Wagner-Murray-Dingell Bill and the Maternity and Child Health Act of 1945.

It was suggested that the members of the American Academy of Pediatrics might be interested in having these principles made available to them through your department in the JOURNAL.

Sincerely yours,

(Signed) STEWART H. CLIFFORD, M.D.

BASIC PRINCIPLES ADOPTED BY THE MASSACHUSETTE MEDICAL SOCIETY WHICH SHOULD GOVERN MEDICAL-CARE PLANS

The objective of adequate medical care in our free society is to make available to everyone—regardless of race, color, creed, financial status or place of residence—every known essential preventive, diagnostic and curative medical service of high quality. The attainment of such medical care must necessarily be an evolutionary process which will require the co-operation of all concerned over a period of years.

The success of any plan for medical care is dependent on the mutual co-operation of the public, those rendering professional services and the administrative agencies. This co-operation can be obtained only if those rendering the services are convinced that they will have a continuing authoritative voice in the formulation and execution of policies and plans, thereby assuming their proper share of responsibility.

Provision of adequate medical care for those unable to obtain it by voluntary prepayment plans or by direct payment is the responsibility of the local or state government. Part of the burden of this responsibility may be assumed by charitable agencies. Federal grant-in-aid to state programs administered by state boards of health is an acceptable method of helping to meet this responsibility.

The medical care of those who are able to purchase it by voluntary prepayment plans or by direct payment is the responsibility of the individual.

Eligibility for receiving benefits under a program aided by federal grants should be determined by the individual states.

The patient shall have free choice of his physician, group of physicians, clinic or hospital from among those participating in any plan, provided that the physician, group of physicians, clinic or hospital shall have the right to refuse or to accept the patient.

Physicians and other qualified persons rendering medical care shall receive adequate remuneration for their services.

The physician shall be free to elect or reject without prejudice participation in a medical care plan. The rights of the physician as to the choice of methods by which he is to be paid shall be fully protected.

The Massachusetts Medical Society looks upon these basic principles as essential to the development of any successful medical care plan and, as guides by which to evaluate medical care plans that may be proposed in the future, with the understanding that changing conditions may require their later revision.

THE SOCIETY LOOKS AT THE WAGNER-MURRAY-DINGELL BILL (SENATE 1606) AND THE MATERNITY AND CHILD WELFARE ACT OF 1945 (SENATE 1318)

Senators Wagner and Murray introduced the National Health Act of 1945—Senate 1606—in the United States Senate on November 19, 1945, the day on which the President's message dealing with this subject was read to the Congress.

The interest of the Massachusetts Medical Society is largely centered in titles one and two of the act.

Title one authorizes grants-in-aid to states to extend the public health services, to increase maternal and child health services and to provide medical care for the needy.

Title two makes provisions for full medical, dental, nursing and laboratory care and hospitalization for those able to pay for such services.

The Massachusetts Medical Society with regard to title one, part A, cites the progressive leadership that the physicians of New England have always shown in the development of public health enterprises, and its adoption as a principle the making available to everyone, every known essential, preventive, diagnostic and curative medical service of high quality. We do approve in general this part of the bill as written, with the following exceptions:

The responsibility for the training of personnel should be the duty of the states and not that of the federal government, as designated in section 314*A*.

Provision should be made which would ensure proper representation of the professional organizations on the advisory council—section 314*F*.

Responsible private agencies, such as the Blue Cross and the Blue Shield, should be included among those with whom the state health agency may make working agreements—section 314*H*.

The state administrative agency should be required to consult with professional advisory committees before issuing regulations, which in turn should be issued only after due notice—section 314*H*.

The Society believes that the objective of title one, part B is more clearly covered in Senate Bill 1318.

With respect to title one, part C, the Society approves of federal grant to aid the several states in assuming their responsibility of providing medical care for those unable to pay for such services. It approves, in general, of this part of the bill as written with the following exceptions:

Federal grants-in-aid for the medical care of needy persons should be made by the United States Public Health Service to state departments of public health.

It disapproves of the provision that places the responsibility in the Social Security Board on the federal level and in the department of welfare on a state level—section 131.

The Society through its Blue Shield having approved of the service principle rather than the payment to patients of cash benefits for medical care, disapproves of the provision in the bill which makes cash payments to individuals for this purpose.

Title two is compulsory health insurance. It would be very costly to carry out the provision of this section of the bill, and there is nothing to intimate what this will add to the burden of the taxpayer or how the money will be raised. Since the Society believes that the payment for medical care of those able to pay for such services by direct payment or on a prepayment basis is the responsibility of the individual and that with the extension and development of voluntary or other plans particularly adapted to certain areas, medical care of the highest quality can be obtained at a reasonable cost, it disapproves of this section.

The Maternal and Child Welfare Act of 1945—Senate 1318—is designated as an act "to provide for the general welfare by enabling the several states to make adequate provision for the health and welfare of mothers and children and for services to crippled children."

The Society finds serious objections to this bill as written. Some of the more important of these are as follows:

The bill makes no adequate provision for general public health programs that are more fundamental than this specialized legislation.

Services and facilities are available to all who elect to participate, regardless of economic status. (This violates Basic Principles 4 and 5.)

The public deserves a reasonable estimate concerning the ultimate cost of this proposed legislation. Experience and such factual data as are available indicate an ultimate annual budget approximating one billion dollars. This should be clearly recognized in any consideration of the bill.

Fee-for-service method of payment is restricted to consultation or emergency visits and is not ordinarily available to practitioners or specialists.

The bill does not make clear just who is to decide the fee for a given service that would be considered adequate remuneration in an individual state, nor does it make provision for variable fees to meet the differing costs in the several states.

The bill does not prohibit professional personnel, groups or institutions rendering service under the program from accepting supplemental payment from or on behalf of patients.

The bill does not provide for payment to groups of physicians, clinics, or hospitals providing professional services.

The bill does not emphasize the desirability of full utilization and further development of existing services and facilities.

The bill does not emphasize the necessity of restricting the development and expansion of a state program to the capacity of available administrative and professional resources.

The bill does not provide the professions with a continuing authoritative voice in the formulation of policies and plans. Such committees as are selected under the provisions of the bill may represent the attitude of the administrator rather than that of a given profession or group. (This violates Basic Principle 2.)

The bill does not provide the facilities whereby the opinions of both the federal and state advisory committees are made available to the public.

Designation of the Children's Bureau as the administrative agency does not adequately assure proper integration of the health activities of the federal government.

For these reasons the Society believes that this proposed act does not represent the best form of legislation for the purposes for which it was written.

Comment

THE ACADEMY GROWS UP

Certain developments at the Pittsburgh meeting evidenced that our 15-year-old child is rapidly growing up and is fast approaching maturity. During these fifteen years of infancy and childhood it has been coddled, guided, admonished, and bossed by its Evanston mother with the love that is necessary for every child during these growing years. As a result it is now ready to stand on its own feet and face the world for better or worse. To one who, as Editor of the JOURNAL, has been in close contact with the Academy for these fifteen years, there were three developments at Pittsburgh whose significance may be overlooked by many who have not had the same opportunity for observation of the child's growth. All three are, in a way, interrelated.

The first was the announcement of a new Committee for the Improvement of Child Health of nine appointed by the President, with three members to be appointed each year for a term of three years. While the primary purpose of this committee is to take over where the "Study Committee," which has been doing such a remarkable job under Dr. Sisson's chairmanship and Dr. Hubbard's Executive direction, leaves off, its importance for the future is even greater. The Academy in the past has not had a definite policy or program, but has of necessity met new developments on a specific basis and at times has been quite unprepared to grasp the significance and potentialities of the problem. This new committee is splendid in its make-up, containing outstanding leaders, and is representative of the various pediatric interests. It will not, like the Executive Board, be forced by necessity to devote most of its time to the mechanics of running the Academy which leaves little time to consider and discuss policies. The value and strength of this committee will depend in large measure upon the wisdom of the new yearly appointments made by the presidents in the future.

The second was the redistribution of the Academy on a basis of membership. The Executive Board is now comparable to the House of Representatives rather than the Senate, and hence becomes much more democratic and directly representative of the membership. Our Executive Board over these years has been made up of a splendid group of men who have been willing to sacrifice of their time and energy for the Academy. It was because of this willingness and ability to work for the Academy that they ultimately found themselves members of the Board. However, it has never been what might be regarded as representative of pediatrics as a whole. With a "policy" committee with the primary purpose of studying and considering the welfare of pediatrics, and an Executive Board to consider the welfare of the Academy, we should be able to make sound progress. The work of the two, as we said before, is closely related.

The third matter of significance was the meeting of the revamped Committee on Legislation. Its chairman has done yeoman service in the past, but has had

to go it very much alone, attempting to represent what he felt to be the opinion and policy of the Academy, when, as a matter of fact, it had no formal policy or united opinion. New and interested young blood has been added to the committee and, with the new "policy" committee as well as the Executive Board to fall back upon, the strength and importance of the Committee on Legislation have increased many, many times.

At a well-attended luncheon meeting of the Committee on Legislation, the point was made that we had no standards or criteria upon which to judge or pass an opinion on the good or bad of proposed legislation. In the discussion it was brought out that the similar point was made at a meeting of the Massachusetts Medical Society. A committee was appointed by them, reflecting all shades of social and economic thought, and this committee found itself able to agree unanimously upon certain fundamental standards or criteria by which legislative proposals should be judged. It was the feeling of everyone present at the luncheon that some such basis or standards should be made for the Academy. This is a matter the Editor feels to be of vital importance to the Academy. In this issue under Social Aspects of Medicine we have reprinted the standards adopted by the Massachusetts Medical Society and the interpretation of two bills under these standards. We feel it is most important for every Fellow to read this section. Had such standards been available and in effect a year or so ago, it would have prevented the somewhat intemperate discussions that took place.

Developments such as these give evidence that the Academy is approaching maturity.

B. S. V.